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=> S THIAZOLIDINEDIONE? AND DIABETES
          1248 THIAZOLIDINEDIONE?
         24504 DIABETES
L1         722 THIAZOLIDINEDIONE? AND DIABETES

=> S L1 AND VANADIUM? AND CHROMIUM?
         39970 VANADIUM?
        106644 CHROMIUM?
L2           4 L1 AND VANADIUM? AND CHROMIUM?

=> D L2 1-4 BIB, KWIC

L2   ANSWER 1 OF 4  USPATFULL
AN     2003:113528  USPATFULL
TI     Biguanide and sulfonylurea formulations for the prevention and treatment
       of insulin resistance and type 2 diabetes mellitus
IN     Pearson, Don C., Lakewood, WA, UNITED STATES
       Richardson, Kenneth T., Anchorage, AK, UNITED STATES
PA     ChronoRX, LLC, Anchorage, AK, UNITED STATES (U.S. corporation)
PI     US 2003078269      A1   20030424
AI     US 2002-93476      A1   20020307 (10)
PRAI   US 2001-278270P     20010322 (60)
       US 2001-278271P     20010322 (60)
       US 2001-278296P     20010322 (60)
DT     Utility
FS     APPLICATION
LREP   TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH
       FLOOR, SAN FRANCISCO, CA, 94111-3834
CLMN   Number of Claims: 130
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 4927
TI     Biguanide and sulfonylurea formulations for the prevention and treatment
       of insulin resistance and type 2 diabetes mellitus
AB     . . . effectiveness, efficiency and safety of the included biguanide
       (metformin) and/or sulfonylurea in the prevention and treatment of
       insulin resistance and diabetes mellitus. The carefully chosen
       additional active ingredients of the invention are designed in a modular
       fashion to prevent and rectify adverse events associated with insulin
       resistance syndrome and diabetes mellitus, and those adverse
       incidences associated with the concurrent use of metformin and/or the
       sulfonylureas. When clinically administered, the invention. . . alone
       or in combination, and broaden their usefulness. The invention will
       retard the progression of insulin resistance to type 2 diabetes
       , and reduce the serious microvascular and macrovascular complications
       commonly associated with insulin resistance syndrome and
       diabetes mellitus.
SUMM   . . . concert with one or more other active ingredients, for use in
       the pharmacological treatment of insulin resistance and type 2
       diabetes mellitus.
SUMM   [0005] Insulin resistance and non-insulin-dependent diabetes
       are prevalent in up to 35% of the population depending upon the age and
       nature of the subset. In the United States alone, 16 million people have
       type 2 diabetes and 13 million have impaired glucose
       tolerance. In fact type 2 diabetes has reached epidemic
       proportions worldwide. By 2025, an estimated 300 million people will
       have diabetes, most of who will inhabit China, India, and the
       United States. Because of an aging and increasingly sedentary, obese
       population. . . unhealthy diets, insulin resistance is also
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increasing alarmingly (it is already two to three times more prevalent than type 2 **diabetes**). This apparent increase in the prevalence of insulin resistance and type 2 **diabetes** occurs in all ethnic populations, but especially in those that have migrated from their native lands to more urbanized and. . .

SUMM [0006] Insulin resistance and type 2 **diabetes** exist not merely as part of the aging process, but also as a process that advances aging. **Diabetes** affects metabolism in totality: carbohydrate, lipid and protein. Its causes and its management are very, very complex and strikingly nonlinear.

SUMM [0007] Patients with **diabetes** of all types have considerable morbidity and mortality from microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (heart attacks, stroke, peripheral vascular. . . leading cause of blindness in the United States) and/or macular edema occur in about 50% of patients with type 2 **diabetes**, as do peripheral and/or autonomic neuropathy. b) The incidence of diabetic renal disease is 10% to 50% depending on ethnicity.. . . Diabetics have heart attacks, strokes and peripheral vascular disease at about triple the rate of non-diabetics. The cost of treating **diabetes** and its complications exceeds $100 billion annually. In addition to these dreadful data, insulin resistance (a prelude to type 2 **diabetes** in about 50% of those effected) with its associated hypertension, coagulopathy, dyslipidemia and obesity substantially adds to these morbidity, mortality. . .

SUMM [0008] There are two clinical forms of **diabetes**, each with a different pathogenesis: type 1, insulin dependent **diabetes** mellitus and type 2, non-insulin dependent **diabetes** mellitus. The latter represents 90% of all diabetics. In type 2 **diabetes** , cellular resistance to the functional effectiveness of insulin results in above normal levels of insulin secretion. When this compensatory increase. . . increases further, blood sugar rises, lipid and protein metabolism are disturbed, and the insidious processes of vascular complications of long-term **diabetes** begin.

SUMM [0009] The fasting hyperglycemia of type 2 **diabetes** exists in the presence of hyperinsulinemia; this reflects the presence of insulin resistance in the liver with resultant glycogenolysis and. . .

SUMM [0012] Free radical generation and induced nitric oxide synthase (iNOS) production secondary to the hyperglycemia of type 2 **diabetes** can lead to pancreatic .beta.-cell destruction, and the production of diagnostic enzymatic indicators characteristic of type 1 **diabetes**. This fact has introduced the term "type 1.5 **diabetes**". In this scenario, .beta.-cells are not only "exhausted" by the progression of pathology from insulin resistance to type 2 **diabetes**, but may also undergo destruction induced by chronic hyperglycemia.

SUMM [0013] Hypertension, dyslipidemia, coagulopathy, obesity and development of type 2 **diabetes**--all of which may follow chronic insulin resistance--are largely preventable, as are the eventual diabetic micro- and macrovascular complications. In those patients with insulin resistance who do progress to type 2 **diabetes**, successful treatment requires maintenance of blood glucose at a normal preprandial level (or at a postprandial level below 180 dl). . .

SUMM . . . Microproteinuria, due to its inadequacy in the glomerular basement membrane, is one of the earliest, most consistent early signs of **diabetes**, and diabetic nephropathy is invariably associated with progressive proteinuria. Reductions of heparan sulfate in the basement membrane of retinal and. . .

SUMM . . . to many disorders associated with aging, i.e., hypertension, obesity, atherosclerosis, lipid abnormalities, coagulopathies and chronic metabolic perturbations including type 2 **diabetes**.

SUMM [0016] Although insulin resistance and type 2 **diabetes** each have an inherited pathogenic component, they both are substantially

influenced by inappropriate diet and inadequate exercise.

SUMM [0017] In aging, as in **diabetes**, elevated circulating glucose reacts nonenzymatically with proteins and nucleic acids to form products that: 1) disturb the functionality of the. . .

SUMM [0018] The ingestion of sugars, fats, and sodium has been linked to insulin resistance, while caloric restriction, exercise, ingestion of **chromium**, **vanadium**, magnesium, and certain antioxidants are associated with greater insulin sensitivity. Lifespan may favorably be affected, and the incidence of many chronic disorders commonly associated both with aging and with **diabetes** can be reduced, by manipulating the diet and its influence upon the glucose/insulin system.

SUMM [0019] **Diabetes**--Pertinent Anatomy and Physiology of Glucose Metabolism

SUMM . . . response) of .beta.-cells to the small amount of insulin that is present may ultimately lead to clinically overt type 2 **diabetes** and its more serious, often devastating complications. (See below.)

SUMM . . . glucose translocation into cells, insulin stimulates cellular uptake of potassium and ascorbate. Thus, when combined with the usual hypomagnesmia of **diabetes**, insulin deficiency exaggerates or cause hypertension and the "tissue scurvy" commonly associated with type 2 **diabetes**.

SUMM . . . to the interplay of two or more signaling processes that result in reciprocal modulation. In the treatment of type 2 **diabetes**, the ability of caveolae to sequester molecules provides a target for influencing both imported and locally produced molecules in the. . .

SUMM . . . in glucose transport and GLUT4 vesicle translocation. It should be noted here that the antihyperglycemic effect of the trace element **vanadium** may in part be due to direct activation of the insulin receptor and in part to a prolongation of the. . .

SUMM . . . Mg.sup.2+ as a cofactor. Mg.sup.2+ deficiency is sufficiently common in diabetics that its oral supplementation is recommended by the American **Diabetes** Association for diabetics with normal renal function.

SUMM [0047] Pancreatic .beta.-cell apoptosis is responsible for irreversible progression toward insulin dependence in type 2 **diabetes**.

SUMM . . . in these processes. The inadequacy or lack of such modulation at multiple points may eventually lead to overt type 2 **diabetes** itself. The identification and influence of these modulation points represent therapeutic opportunities and underly the rationale of this invention.

SUMM [0056] Although circulating insulin levels are frequently elevated early in type 2 **diabetes**, a deficiency of intracellular insulin and increased cellular resistance to many of insulin's actions simultaneously occur: there is resistance to. . .

SUMM . . . the adipocytes of obese individuals, and that this TNF-.alpha. is a principal contributor to insulin resistance and subsequent type 2 **diabetes** in obese patients. TNF-.alpha. is an important regulator of the processes of apoptosis and thus modulates the volume of tumor,. . .

SUMM [0060] It is clear that the process governing both insulin resistance and type 2 **diabetes** is diagrammatically syncytial. It is not a linear, straightforward process that lends itself to a single treatment modality. Neither disease. . .

SUMM [0061] Aging and **Diabetes** Mellitus

SUMM . . . insulin at its receptor site and a decreased response by the pancreatic .beta.-cells to glucose levels. In aging, similar to **diabetes**, the elevated circulating glucose secondary to increasing insulin resistance reacts nonenzymatically with proteins and nucleic acids to form products that. . . from elevated free radical formation resulting from the autooxidation of glucose. Augmented free

radical formation and lipid peroxidation, common in **diabetes** mellitus, are associated with the "premature aging" of diabetic patients. Long term, excessive ingestion of sugars, fats and sodium have been linked to decreased insulin sensitivity, while caloric restriction, exercise, ingestion of **chromium**, **vanadium**, Mg.sup.2+, certain free radical scavengers and nuclear factor kappa B (NFkappaB) inhibitors are associated with greater insulin sensitivity. Thus, manipulation. . . the glucose/insulin system may favorably affect lifespan and reduce the incidence of the microvascular and macrovascular complications of type 2 **diabetes**.

SUMM [0064] The earliest microvascular lesion of **diabetes** is a variable thickness of the basement membrane. A healthy basement membrane provides vascular stability and importantly, a permeability barrier.. . . acid, n-acetylcysteine (NAC) and possibly taurine, may contribute to the adequacy of this necessary negativity of the cell membrane. In **diabetes** both the basement membrane thickness and heparan sulfate levels are decreased. As a result, vessel permeability is increased. Increased vessel permeability is the most notable initial microvascular complication in **diabetes**.

SUMM [0065] Early in **diabetes** there are additional abnormal microvascular (arteriolar and capillary) dysfunctions: e.g., intraluminal pressure and flow are both increased: these changes, plus. . .

SUMM [0068] 2. Diabetic nephropathy is common in type 2 **diabetes**. Risk of death is increased 100 fold.

SUMM [0082] Although **diabetes** mellitus and insulin resistance are progressive, complex and frequently unpredictable processes with many points of potential instability, the latter are identifiable. To have any long-term chance of favorably influencing the cellular pathophysiology of insulin resistance and type 2 **diabetes**, any clinical approach must involve not only the coordination of life style modification, but also utilize finely calibrated combinations of. . .

SUMM [0083] Therefore it is useful to consider, in turn, the pathologic states caused by insulin resistance and type 2 **diabetes**, the underlying molecular biologic defects or deficiencies, the existing modalities for favorably modulating these and the complementary, beneficial interactions of. . .

SUMM [0084] A. Pathologic States Caused by or Worsened by Insulin Resistance and/or Type 2 **Diabetes**

SUMM [0101] B. Cellular Physiological and Molecular Biological Disturbances in Insulin Resistance and/or Type 2 **Diabetes**

SUMM . . . drugs are currently available: biguanides (e.g., metformin), sulfonylureas (e.g., tolbutamide, glyburide, glipizide and others),.alpha.-glucosidase inhibitors (e.g., acarbose and miglitol) and **thiazolidinediones** (e.g., troglitazone and rosiglitazone), each of these has a different mode and site of action.

SUMM . . . concurrent use of both (i.e., a combination of sulfonylurea and biguanide) for treatment of progressive insulin resistance and type 2 **diabetes**.

SUMM [0147] The principle of long-term maintenance of glucose control applies to both progressive insulin resistance and type 2 **diabetes**. The treatment strategies while similar, are somewhat different. Progressive insulin resistance has as its central abnormality hyperinsulinemia. The latter persists as the disease progresses to type 2 **diabetes** with its central abnormality, hyperglycemia. In each case the process is nonlinear and its pharmacological modulation is complex.

SUMM . . . the associated defects in insulin secretion. This not only has direct implications for adequate classification and treatment of type 2 **diabetes** in the elderly, but also for understanding the autoimmune/inflammatory mechanisms involved in the pathogenesis of hyperglycemia.

SUMM . . . .beta.-cell apoptosis, this invention will enhance the effectiveness of sulfonylurea therapy by stopping or slowing the progression of type 2 **diabetes** toward this stage of progressive autoimmune/inflammatory .beta.-cell destruction--sometimes referred to as "type 1.5" **diabetes**.

SUMM . . . unsatisfactory. It is the intention of this invention to extend the duration of effect of sulfonylurea treatment of type 2 **diabetes** by delaying the onset, and slowing the progression of .beta.-cell dysfunction and inappropriate .beta.-cell apoptosis.

SUMM . . . with higher initial glucose concentrations, those who are younger, those with lower .beta.-cell reserve and in the United Kingdom Prospective **Diabetes** Study (UKPDS) those randomized to second generation drugs, compared with first generation drugs . Prospective placebo-controlled trials have shown that. . .

SUMM [0170] Regarding the benefit of intensive therapy with sulfonylureas (chlorpropamide, glibenclamide) or with insulin in type 2 **diabetes**, the UKPDS interpreted their data to indicate that ". . . intensive blood glucose control by either of the sulfonylureas. . .

SUMM [0171] Management of patients with progressive insulin resistance and type 2 **diabetes** should focus on decreasing the excess macrovascular disease with which these are associated, as well as preventing or minimizing microvascular. . . However, this requires the concomitant management of the cardiovascular risk factors of the insulin resistance syndrome associated with type 2 **diabetes**: e.g., a reduction of the macrovascular-disease-promoting sulfonylurea side effect of carnitine depletion and/or a reduction of metformin-induced hyperhomocysteinemia.

SUMM [0175] Type 2 **diabetes** mellitus is part of a complicated metabolic-cardiovascular pathophysiologic cluster alternately referred to as the insulin resistance syndrome, Reaven's syndrome, the metabolic syndrome or syndrome X. Since the macrovascular coronary artery disease associated with insulin resistance and type 2 **diabetes** is the major cause of death in the latter, it is desirable that any hypoglycemic agent favorably influences known cardiovascular. . .

SUMM . . . independent of their hypoglycemic properties. These additional actions may be useful in preventing or attenuating the long-term vascular complications of **diabetes**, e.g., diabetic retinopathy. While the favorable effect of reducing platelet aggregation seems established, a disturbing recent study shows an increase. . .

SUMM . . . in the homeostasis of other amino acids for which deficiencies should be avoided in progressive insulin resistance and type 2 **diabetes**, e.g., taurine and L-arginine. Given these renal effects of the sulfonylureas, it is not surprising that there macrovascular benefits are. . .

SUMM [0194] The controversial results of the University Group **Diabetes** Program study (1970) suggested that sulfonylureas might exacerbate coronary artery disease in patients with type 2 **diabetes**. Subsequent clinical trials have not demonstrated these increased cardiac mortality rates in diabetic patients actually treated with sulfonylureas. In fact, the UKPDS found no increased incidence of coronary artery disease in those patients with type 2 **diabetes** , who were assigned to intensive therapy with sulfonylureas, when compared with patients receiving diet therapy. There is no published data to support an advantage of any one sulfonylurea with respect to coronary artery disease. An American **Diabetes** Association policy statement opposes any formal restrictions based on the interpretations of the University Group **Diabetes** Program findings.

SUMM . . . maximized, safety improved and the scope of beneficial effects broadened in progressive insulin resistance, insulin resistance syndrome and type 2 **diabetes** when delivered in the formulations of this invention.

SUMM [0198] A.6. Use of the Invention for the Prevention and Treatment of Insulin Resistance Syndrome and Type 2 **Diabetes** (Sulfonylurea+Other Active Ingredients)

SUMM . . . As illustrated by the foregoing list of cellular physiological and molecular biological disturbances, both insulin resistance syndrome and type 2 **diabetes** are progressive, complex, dynamic metabolic system failures with potential instability at many points. Its genesis is in part related to. . . known to be detrimental to persons with the potential for developing (or who already have) insulin resistance or type 2 **diabetes**. This physiological modulation is achieved by the formulations of this invention and is the basis for their improvement in the. . .

SUMM [0200] As an individual progresses toward and into type 2 **diabetes**, an increasing number of specific complementary biomolecules, biofactors and trace elements are necessary to compliment sulfonylureas, as shown in the. . . be pointed out that a "shotgun" approach that throws everything in the biochemical bible at insulin resistance or type 2 **diabetes** not only is illogical, unnecessary and expensive, but also may be detrimental. Errors of commission in this regard are as. . .

SUMM . . . one of its active ingredients, a sulfonylurea for use in the prevention and treatment of insulin resistance and/or type 2 **diabetes**. The preparation contains elements of specific, sometimes unique, therapeutic biomolecules, biofactors and trace elements selected because of their particular and. . .

SUMM [0202] In the United States alone, 16 million people have type 2 **diabetes** and a substantial multiple, perhaps 4.times. to 5.times., are insulin resistant--at least one-half of these are undiagnosed. Type 2 **diabetes** is preceded by a long period of insulin resistance, impaired glucose tolerance and a reversible metabolic state associated with an. . .

SUMM [0203] Susceptibility to type 2 **diabetes** requires both genetic (most likely polygenic) and acquired factors. Its continuing pathogenesis involves an interplay of progressive cellular insulin resistance and pancreatic .beta.-cell failure. Any ideal treatment of type 2 **diabetes** must reduce insulin resistance and .beta.-cell dysfunction in a majority of treated patients and prevent, delay, or reverse the long-term. . .

SUMM . . . action in order to provide for better sulfonylurea management of the insulin resistance syndrome, more efficient prevention of type 2 **diabetes**, better management of type 2 **diabetes** and for prevention of long-term macrovascular and microvascular complications.

SUMM [0206] The complexity of type 2 **diabetes** pathophysiology provides the opportunity to expand sulfonylureas' clinical usefulness by the administration of complementary, novel combinations of biomolecules, biofactors and. . .

SUMM . . . member of the sulfonylurea family of drugs combined with elements to enhance treatment of progressive insulin resistance and type 2 **diabetes**. This invention addresses sulfonylurea-induced mitochondrial malfunction and the failure of sulfonylurea to prevent diabetic macrovascular disease. It improves the useful. . .

SUMM [0235] Metfornin has a unique mechanism of action and controls glycemia in both obese and normal-weight, type 2 **diabetes** patients without inducing hypoglycemia, insulin stimulation or hyperinsulinemia. It prevents the desensitization of human pancreatic islets usually induced by hyperglycemia. . .

SUMM . . . eliminated primarily by renal filtration and secretion and has a half-life of approximately 6 hours in patients with type 2 **diabetes**; its half-life is prolonged in patients with renal impairment. It has no effect in the absence of insulin. Metformin is as effective as the sulfonylureas in treating patients with type 2 **diabetes**, but has a more prominent postprandial effect than

either the sulfonylureas or insulin. It is therefore most useful in managing. . .

SUMM [0240] Except perhaps for its appearance in aging, insulin resistance and type 2 **diabetes** do not usually occur in isolation, but as part of the complex metabolic-cardiovascular `Syndrome X`, mentioned previously. Hyperinsulinemia and hyperglycemia. . . avoided. Long-term prospective studies have shown that treatment of hypertension and dyslipidemia reduces cardiac events in patients with type 2 **diabetes**. As an example, the United Kingdom Prospective **Diabetes** Study (UKPDS) showed that improved control of blood pressure reduced not only macrovascular complications (heart attacks, strokes, and death), but. . . to their improvement. Because obesity and physical inactivity are global risk factors for coronary artery disease as well as for **diabetes**, the need for weight loss and exercise must be stressed when **diabetes** initially is diagnosed, and must be reinforced throughout the natural history of the disease. However, modification of these may not. . .

SUMM . . . hyperinsulinemia, metformin improves levels of plasminogen activator inhibitor (PAI-1) and thus improves fibrinolysis in insulin resistance patients with or without **diabetes**. Weight gain does not occur in patients with type 2 **diabetes** who receive metformin; in fact, most studies show modest weight loss (2 to 3 kg) during the first 6 months. . .

SUMM . . . various elements of the insulin resistance syndrome help define its usefulness in the treatment of insulin resistance and type 2 **diabetes**. These useful effects are enhanced when metformin is combined with components of this invention. The latter increase its effectiveness and. . .

SUMM [0246] Unquestionably the UKPDS established that type 2 **diabetes** is a progressive disorder. Ideally, treatment with metformin (or a sulfonylurea, or insulin) would halt the progressive deterioration of glycemic. . . in glycemic control is relentless. In the UKPDS, this decline was related to deterioration of .beta.-cell function. The University Group **Diabetes** Program study similarly confirmed the progressive nature of type 2 **diabetes**. These important studies emphasize the need for constant reassessment of patients with insulin resistance and/or **diabetes**, and for appropriate adjustment of the therapeutic regimen in order to avoid hyperinsulinemia, deterioration or apoptosis of .beta.-cells and progressive. . .

SUMM . . . reducing the risks associated with specific abnormalities of several conditions and functions frequently associated with insulin resistance and/or type 2 **diabetes**. These include, among others, dysfunctional vascular endothelium, inappropriate apoptosis, undesirable platelet agglutination, inadequate maintenance of cell volume, dyslipedemia, hyperhomocysteinemia, .beta.-cell. . .

SUMM [0256] B.4. Use of the Invention for the Prevention and Treatment of Insulin Resistance Syndrome and Type 2 **Diabetes** (Metformin+Other Active Ingredients).

SUMM [0257] As an individual progresses from often-covert insulin resistance toward and into type 2 **diabetes**, and has a corresponding need for drug therapy, metformin is often the drug of choice. However, because of limitations upon. . .

SUMM . . . oral dosage forms which will increase the effectiveness, efficiency and safety of the treatment of insulin resistance and/or type 2 **diabetes**. In addition to metformin, the invention contains specific, sometimes unique, therapeutic biomolecules, biofactors and trace elements selected because of their particular and critical, combinational physiological effects in reducing adversities commonly associated with insulin resistance, type 2 **diabetes** and clinical biguanide use.

SUMM . . . action in order to provide for better metformin management of

the insulin resistance syndrome, more efficient prevention of type 2 **diabetes**, better management of type 2 **diabetes** and for prevention of long-term macrovascular and microvascular complications.

SUMM [0274] Preventing progression from type 2 to "type 1.5" **diabetes** .

SUMM . . . metformin and other active ingredients for clinical use directed at enhancing the treatment of progressive insulin resistance and type 2 **diabetes**. By various means the invention will increase the number of patients who will benefit from metformin therapy.

SUMM . . . provide concurrent complementary support for a widened spectrum of patients who are at risk of insulin resistance and type 2 **diabetes**, including those who require both metformin and sulfonylurea in combination.

SUMM . . . carnitine renal loss) tend to normalize the mitochondrial fuel supply. Taurine, often low in progressive insulin resistance and type 2 **diabetes**, is required to move Ca.sup.2+ into the mitochondria to signal ATP production. Magnesium is also necessary in the modulation of. . .

SUMM . . . spiral of, vascular degradation, local hypoxia, thrombogenesis and atrophy/apoptosis causing the macrovascular complications of progressive insulin resistance and type 2 **diabetes**.

SUMM . . . intracellular defense against free radicals generated by mitochondrial metabolism and excess free radicals secondary to hyperglycemia. It becomes depleted in **diabetes**. Metformin increases available GSH in both diabetics and non-diabetics, indicating that it has some antioxidant activity that is independent of,. . .

SUMM [0301] Tetrahydrobiopterin (BH4) is an essential cofactor for nitric oxide synthase. In low concentrations of BH4, as is common in **diabetes**, nitric oxide synthase produces less constitutive NO and, correspondingly, larger quantities of the superoxide anion and hydrogen peroxide.

SUMM [0302] Excessive pancreatic .beta.-cell apoptosis is responsible for the irreversible progression toward insulin dependence found in type 2 **diabetes**. The integrity of the mitochondrial membrane is essential for preventing .beta.-cell dysfunctional apoptosis. The components of this group will inhibit. . .

SUMM [0305] Nocturnal occurrences of myocardial ischemia/reperfusion events are common in progressive insulin resistance and type 2 **diabetes** , and the post-infarction mortality rate in these patients is double that of non-diabetics. Bedtime therapy, as defined in this invention,. . .

SUMM [0306] The increased incidence of nocturnal myocardial ischemia and arrhythmias in progressive insulin resistance and type 2 **diabetes** relates to: (1) hypertension, (2) a blunted nocturnal fall in blood pressure, (3) hypoxemia induced by sleep apnea, (4) autonomic neuropathy, and (5) thrombogenesis. These are often interrelated. For example: in hypertension, sleep apnea syndrome and **diabetes** the normal nocturnal fall in blood pressure is absent or reversed. As another example: progressive insulin resistance causes hypertension and. . .

SUMM [0308] IV. Insulin Alternative Group

	Dosages in Milligrams: Preferred	Most Preferred
Vanadium	7.5-375	25-150
L-Arginine	75-3125	250-1250
Chromium	0.01-0.63	0.03-0.25
Zinc	1.5-125	5-50

SUMM [0312] **Vanadium** mimics insulin intracellularly and prolongs

insulin action. It increases both hepatic and peripheral insulin sensitivity, and activates glycogenesis, decreasing hyperglycemia. **Vanadium** preserves pancreatic .beta.-cells, and decreases diabetic hyperphagia, thereby improving both the safety and effectiveness of sulfonylurea and metformin.

SUMM [0313] **Chromium,** often deficient in **diabetes,** is a cofactor for insulin, increasing its binding to the insulin receptor and reducing insulin resistance. It increases the number. . . .

SUMM . . . invention will reduce sulfonylurea and/or metformin requirements and will prevent or delay the need for injectable insulin in type 2 **diabetes**.

SUMM [0318] The molecular complexes of this invention address various aspects of insulin resistance and type 2 **diabetes** such as 1) mitochondrial metabolism, 2) mitochondrial membrane integrity, 3) plasma membrane integrity, 4) adverse cytokine cascades, 5) dysfunctional .beta.-cell. . .

SUMM . . . increase the effectiveness, efficiency and safety of metformin and/or sulfonylureas in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus. They have the following formulae:

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SUMM . . . increase the effectiveness, efficiency and safety of metformin and/or sulfonylureas in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus.

SUMM . . . containing sulfonylurea, metformin or metformin-sulfonylurea combinations with active, complementary ingredients in the treatment of progressive insulin resistance and type 2 **diabetes**. The invention describes combinations of specific, sometimes unique, therapeutic biomolecules, biofactors and trace elements selected because of their particular and. . .

SUMM [0404] Type 2 **diabetes** is preceded by a long period of impaired glucose tolerance and a reversible metabolic state associated with an increasing prevalence. . . the time of diagnosis, long-term complications have already developed in almost one fourth of these patients. Susceptibility to type 2 **diabetes** requires both genetic (most likely polygenic) and acquired factors. Its continuing pathogenesis involves interplay between progressive cellular insulin resistance and pancreatic .beta.-cell failure. Any ideal treatment of type 2 **diabetes** must reduce insulin resistance and .beta.-cell dysfunction in a majority of treated patients and, in addition, prevent, delay, or reverse. . .

SUMM [0408] The complexity of progressive insulin resistance and type 2

diabetes pathophysiology, and the nature of the effect of either or both sulfonylurea and of metformin on the disease process, provides. . . biomolecules, biofactors and trace elements, many of which are deficient or functionally inadequate in progressive insulin resistance and type 2 **diabetes**, and some of which are inadequately moderated or worsened by sulfonylurea and/or metformin treatment, the clinical usefulness of the latter. . .

SUMM . . . variety of reasons, many of the components are deficient in persons with insulin resistance and in diabetic patients. Mg.sup.2+, ascorbate, **chromium** and certain amino acids (viz., carnitine, taurine, arginine) are important examples of such diabetic deficiencies, either because of inadequate intake. . .

SUMM [0413] L-arginine is usually limited in insulin resistance syndrome and type 2 **diabetes**; an insufficiency that can be overcome by dietary supplementation.

SUMM . . . and thrombosis, and in improving the dynamic and theological vascular responses in patients with insulin resistance syndrome and/or type 2 **diabetes**.

SUMM . . . L-arginine inhibits lipid peroxidation, additionally protecting the endothelium and reducing long-term microangiopathic complications in insulin resistance syndrome and type 2 **diabetes**.

SUMM . . . administered it increases the effectiveness, efficiency, and safety of combined sulfonylurea-metformin in the prevention and treatment of insulin resistance and **diabetes** mellitus.

SUMM [0423] Diabetics have at least 30% lower circulating ascorbic acid concentrations than people without **diabetes** mellitus. The cellular uptake and cellular level of vitamin C (ascorbic acid, AA) is promoted by insulin and reduced in. . .

SUMM . . . derived directly from inadequate carnitine, the symptoms of weakness and fatigue often seen in progressive insulin resistance and type 2 **diabetes** may relate to carnitine deficient mitochondrial dysfunction, indirectly due to inadequate cytosolic AA.

SUMM . . . generation of reactive oxygen species (ROS) is high and in which ROS production greatly multiplies during pathological processes such as **diabetes**. Normally ROS are effectively protected against by the high capacity of inherent antioxidative systems: enzymes and water- or lipid-soluble low. . .

SUMM . . . from the autooxidation of glucose, hyperglycemia induces oxidative free radical stress. AA has been shown to be highly consumed in **diabetes**, presumably through free radical scavenging. If a continuous supply of AA is available, it indirectly maintains appropriate levels of other. . .

SUMM . . . to L-arginine in lessening endothelial dysfunction by normalizing constitutive NO production in patients with insulin resistance syndrome and/or type 2 **diabetes**. This action of AA improves impaired acetylcholine-induced vasodilation by a mechanism linked to NO formation. AA selectively restores impaired endothelium-dependent vasodilation even in patients with insulin-dependent **diabetes** mellitus

SUMM . . . to causing oxidative stress, hyperglycemia--via glycation of proteins--generates Maillard products that cross-link. These advanced glycation products occur in vivo in **diabetes** mellitus as well as in aging. Activation of the polyol (sorbitol) pathway leads to such nonenzymatic protein glycation that causes. . .

SUMM . . . reducing agents and is an essential cofactor for the enzymatic activity of eNOS. Suboptimal concentration of BH4, as occurs in **diabetes**, reduces formation of NO and "uncouples" eNOS leading to an eNOS-mediated reduction of oxygen, the formation of superoxide anions and. . .

SUMM . . . when L-arginine, is decreased. Thus, eNOS may become a direct source of reactive oxygen species under pathological conditions such as **diabetes**, when either or both may be lacking. Because NO reacts

with the superoxide anion and hydrogen peroxide to form peroxynitrite,. . .

SUMM . . . This is improved by concomitant oral treatment with BH4: Further evidence that endothelial function in insulin resistance and type 2 **diabetes** is modulated by the availability of BH4.

SUMM [0441] Carnitine levels are reduced in **diabetes**, and are further decreased by sulfonylurea treatment.

SUMM . . . fuel; however, glucose may not provide sufficient energy for normal cardiac function, especially in progressive insulin resistance and type 2 **diabetes**. This can lead to severe cardiac arrhythmias, cardiac arrest and death. In addition, the excessive exposure of tissues to fatty. . .

SUMM [0444] As stated, carnitine is deficient in type 2 **diabetes**, and further depleted by sulfonylurea treatment. It is surprising that this important adverse effect--sulfonylurea-induced carnitine deficiency--is seldom referred to. This. . . considers that a major disappointment of sulfonylurea therapy is that it fails to prevent the macrovascular complications of type 2 **diabetes**, presumably, in part because of its adverse effect on carnitine homoeostasis.

SUMM . . . thereby inducing the macrovascular complications associated with carnitine deficiency, which are the same as the macrovascular complications of type 2 **diabetes**: heart attacks, stroke and peripheral vascular disease. Additionally, the reperfusion injury that occurs after a macrovascular ischemic event is worse. . .

SUMM [0447] Serious results from heart attacks, the leading cause of death in type 2 **diabetes**, can be divided into cardiomyopathy, if the area of damage is sufficiently large that the heart can no longer function. . .

SUMM . . . of hepatic fatty acid oxidation by carnitine has considerable clinical potential in patients with both insulin resistance and type 2 **diabetes** although this same activity also tends to enhance hepatic gluconeogenesis, limiting its usefulness to some extent. However, there is also. . .

SUMM . . . carnitine is of enormous physiologic importance, and its deficiency in pathologic states such as progressive insulin resistance and type 2 **diabetes** worsens the outlook. Carnitine is safe and, except for a tendency to increase hepatic gluconeogenesis, it has no side effects. . .

SUMM . . . administered, it increases sulfonylurea-metformin effectiveness, efficiency, and safety in the prevention and treatment of progressive insulin resistance and type 2 **diabetes**, reduces the cardiovascular risks associated with these diseases and reduces adverse side effects which arise from the combined use of. . .

SUMM . . . by transferring one of its methyl groups to homocysteine to form methionine, thereby lessening the threat of homocysteine-induced thrombosis in **diabetes**.

SUMM [0460] **Chromium**

SUMM [0461] There is a dietary deficiency of **Chromium** (Cr) in more than one-half of the USA population.

SUMM . . . fat metabolism. Insufficient dietary Cr has been associated with the development of the insulin resistance syndrome and of type 2 **diabetes**, and with their associated cardiovascular diseases. This dietary shortfall has been exacerbated by the worldwide increase intake of refined foods. . .

SUMM [0464] Cr supplementation improves the diabetic control afforded by exercise. Supplements of **chromium** nicotinate or picolinate complexes lower blood sugar, LDL cholesterol and increase lean body mass. Cr supplementation can reduce metformin requirements. . .

SUMM . . . supplying the necessary cysteine intracellularly. GSH and glutathione peroxidase levels are notably reduced in progressive insulin resistance and type 2 **diabetes**. The deficiencies and the associated peroxide-mediated damage to cell membranes may appear early

in the progressive insulin resistance and type 2 **diabetes**, before the development of secondary complications. Additionally, GSH counterbalances the effects of ICAM-1, one of the most important intercellular adhesion molecules involved with the atherogenesis associated with insulin resistance syndrome and type 2 **diabetes** . GSH similarly reduces thrombin activation, which results from hyperglycemia.

SUMM . . . and other elements of this invention, have the potential to delay the onset and delay the progression of "type 1.5 **diabetes** ". In the latter, ROS destroy pancreatic .beta.-cells. This .beta.-cells destruction results in the addition of insulin-dependent (type 1) **diabetes** mellitus clinical findings to those already existing from type 2 **diabetes**. Activation of NFkappaB by ROS-induced release of mitochondrial cytochrome C seems to be the key cellular signal in initiating a. . . of the prodrug NAC or .alpha.-lipoic acid)--a key intracellular regulator of NF-kappaB--affords protection against the insidious onset of "type 1.5 **diabetes**". In this context, supplementation with 500 mg/kg of NAC as a GSH precursor, has been shown to inhibit alloxan-induced NFkappaB. . . By inference, NFkappaB activation by ROS (via the mitochondria) may initiate a sequence of events eventually leading to type 1 **diabetes**, by way of "type 1.5 **diabetes**": In one study, inhibition of NF-kappaB activation by NAC has been shown to attenuate the severity of type 1 **diabetes**.

SUMM . . . sulfate, which may contribute to its thrombogenic property, which also potentially exacerbates the diminished heparan sulfate synthesis commonly observed in **diabetes** (See above.). A circular problem is therefore initiated in **diabetes**: homocysteine reduces heparan sulfate in the glomerulus, which leads to renal malfunction, which in turn leads to hyperhomocysteinemia, which aggravates the hypertension and thromboangiogenesis of **diabetes** , etc.

SUMM [0477] Hyperhomocysteinemia is associated with macrovascular disease in a significant proportion of patients with type 2 **diabetes**. Furthermore, this hyperhomocysteinemia is related to 5-year mortality rates independent of other major risk factors, and is a stronger (1.9-fold). . .

SUMM . . . that is essential for its structural integrity; the latter results in the vascular leakage associated with the devastating microangiopathies of **diabetes**.

SUMM [0480] **Diabetes** significantly lowers folate in kidney, heart, brain, and muscle. The addition of metformin worsens this situation. For these reasons folate inclusion in a formula with sulfonylurea and/or metformin in progressive insulin resistance and type 2 **diabetes** is logical.

SUMM [0482] .alpha.-Lipoic acid is an important inclusion in sulfonylurea and/or metformin treatment for insulin resistance syndrome and type 2 **diabetes**. It increases insulin sensitivity, prevents depletion of GSH, limits protein glycation and attenuates NFkappaB transcription.

SUMM . . . acid and indirectly regenerates .alpha.-tocopherol. It increases intracellular GSH and limits protein glycation. It has the potential favorably to modify **diabetes** and reduce **diabetes**-induced complications, particularly diabetic neuropathy.

SUMM . . . and AA. .alpha.-lipoic acid seems to reduce AGE albumin-induced NF-kappaB mediated transcription and the expression of relevant endothelial genes in **diabetes**. Among others these include, tissue factors for VCAM-1 and for endothelin-1. Thus, in vitro supplementation of cellular antioxidative defense mechanisms. . .

SUMM . . . of events leading to .beta.-cell death. This, plus .alpha.-lipoate's enhancement of pancreatic GSH, affords protection against progression from type 2 **diabetes** to "type 1.5

diabetes".

SUMM . . . increases the effectiveness, efficiency, and safety of sulfonylurea and/or metformin combinations in the prevention and treatment of insulin resistance and **diabetes** mellitus and expands the scope of sulfonylurea and/or metformin treatment to include macrovascular diabetic complications. Sulfonylurea and/or metformin pharmacokinetics do. . .

SUMM [0492] The American **Diabetes** Association recommends that all patients with normal renal function who have hypomagnesemia and **diabetes** mellitus receive Mg.sup.2+ supplementation. This represents a majority of patients with progressive insulin resistance or type 2 **diabetes**. Mg.sup.2+ deficiencies are widespread in the progressive insulin resistance and type 2 **diabetes**. Patients receiving sulfonylurea exhibit little change in urinary excretion of Mg.sup.2+ yet they show a significant rise in serum Mg.sup.2+.. . .

SUMM . . . sulfonylurea and metformin on magnesium levels is unclear, their pharmacodynamic complementarity for patients with progressive insulin resistance or type 2 **diabetes** is fortunate, since both hyperinsulinemia and hyperglycemia can result in hypomagnesemia, which in turn increases insulin resistance--another vicious cycle.

SUMM [0494] Hypomagnesemia occurs in 25-38% of patients with type 2 **diabetes**. Current dietary amounts of Mg.sup.2+ are marginal. The average dietary intake of 450 to 485 mg per day of Mg.sup.2+. . . population dietary Mg.sup.2+ shortfall of 90 to 180 mg per day. Unfortunately for patients with insulin resistance and type 2 **diabetes**, circulating insulin (and perhaps proinsulin) induce an increase in the renal excretion of Mg.sup.2+. This might partly explain the Mg.sup.2+. . .

SUMM . . . the depletion of free Mg.sup.2+. Mg.sup.2+ supplementation should improve both insulin sensitivity and insulin secretion in patients with type 2 **diabetes**.

SUMM [0496] Decreased cellular Mg.sup.2+ concentrations represent a risk factor in the pathogenesis of both microvascular and macrovascular complications of **diabetes**. Low serum and dietary Mg.sup.2+ may be related to the etiologies of CVHD, hypertension, and atherosclerosis as well as progressive insulin resistance and type 2 **diabetes**. One of the most serious complications of **diabetes**, cardiac irregularity, including ventricular ectopic beats, is associated with decreased intracellular Mg.sup.2+.

SUMM . . . importantly illustrates the synergistic and synergetic relationships that can (and must) be addressed by approaching insulin resistance and type 2 **diabetes** as nonlinear complexities, as is done by this invention.

SUMM [0499] In addition to complementary effects of Mg.sup.2+ with .alpha.-tocopherol and GSH in **diabetes**, similar synergisms for Mg.sup.+ have been defined with taurine, carnitine and **vanadium**, and with sulfonylurea and/or metformin.

SUMM [0501] The inadequate intracellular Mg.sup.2+ concentration often found in progressive insulin resistance and type 2 **diabetes** results in defective tyrosine-kinase activities at the insulin receptor level and exaggerated intracellular Ca.sup.2+ concentration. Daily Mg.sup.2+ administration to type 2 **diabetes** patients restores intracellular Mg.sup.2+ concentration and can contribute to improved insulin-mediated glucose uptake.

SUMM . . . potent antioxidant action similar to SOD. Some studies have shown that melatonin protects against oxidative stress and the severity of **diabetes** induced by STZ. Two activities are becoming apparent: 1) the powerful antioxidant action of this indole and, 2) the importance. . .

SUMM [0506] TNF-.alpha. has an important role in the development of insulin resistance, and type 2 **diabetes** and its progressive vascular complications. It can be favorably modified by melatonin. Cytokine

production, including TNF-.alpha., in human whole blood. . . could fail to reduce the cytokine surge adequately and be detrimental in patients with progressive insulin resistance or type 2 **diabetes** . This may foster well-known, diabetic microvascular and macrovascular complications.

SUMM [0507] Melatonin also reduces the visceral fat that is associated with progressive insulin resistance and type 2 **diabetes**. Thus it is important in enhancing the weight loss potential of metformin.

SUMM [0508] Visceral fat and plasma insulin levels increase with aging, and are associated with progressive insulin resistance and type 2 **diabetes**. Since melatonin favorably modulates visceral fat and the nighttime cytokine surge, its inclusion with metformin and/or sulfonurea is potentially important,. . .

SUMM . . . inducible isoform of nitric oxide synthase (iNOS), an important contributor to the pathophysiology of inflammation, including the macrovascular complications of **diabetes** and pancreatic .beta.-cell destruction. Melatonin reduces iNOS steady-state mRNA levels and iNOS protein. This inhibition of iNOS expression is associated. . . of the transcription factor nuclear factor kappa B (NFkappaB), which has been associated with pancreatic .beta.-cell apoptosis in type 1 **diabetes**.(See above.) Additionally, melatonin decreases the production of nitrite/nitrate (the breakdown products of NO) in macrophages stimulated with bacterial lipopolysaccharide, reducing inflammation. These effects may be important in inhibiting the progression from type 2 **diabetes** to "type 1.5 **diabetes** ", wherein there is an added immunologically driven .beta.-cell destruction superimposed on type 2 **diabetes**.

SUMM . . . of evidence indicates that melatonin production declines after age 45 in parallel with a statistically increasing occurrence of type 2 **diabetes**. It is reasonable to believe that the age-related loss of availability of melatonin and a subsequent reduction in capacity to reduce lipid peroxidation and AGEs, could be detrimental in type 2 **diabetes**. Melatonin is a useful component in metformin and/or sulfonylrea formulations used as treatment for progressive insulin resistance and type 2 **diabetes** is physiologically appropriate, and possibly should be made not only at night, but also during the day.

SUMM . . . both useful for reducing hypertriglyceridemia, thus having complementary potential in treating the dyslipidemia of progressive insulin resistance and type 2 **diabetes**.

SUMM [0514] Nicotinamide has value in preventing .beta.-cells destruction in type 1 **diabetes**. That there are beneficial effects in type 2 **diabetes** is not yet established, but prevention of progression from type 2 **diabetes** to "type 1.5 **diabetes**" seems likely, thus complementing sulfonylurea. Interleukin-1 beta (IL-1 beta) is known to inhibit glucose-induced insulin release by pancreatic islets. When. . .

SUMM . . . can be demonstrated in the circulation. These antibodies can be detected up to eight years prior to overt type 1 **diabetes** and are also seen in some progressing type 2 diabetics (thus the name "type 1.5 **diabetes**"). Nicotinamide, a vitamin B.sub.3 derivative, interferes with the immune-mediated .beta.-cell destruction by reducing the content of free radicals and NO,. . .

SUMM [0518] Unfavorable Theological properties of blood, and abnormal red cell deformability, in **diabetes** are factors in its frequent microvascular complications. The improvements in blood rheology and in red cell deformability by .alpha.-tocopherol nicotinate,. . . membrane of red blood cells. Treatment with .alpha.-tocopherol nicotinate may have complementary effects in slowing the microangiopathy of type 2 **diabetes**.

SUMM . . . (Amadori.fwdarw.Maillard reactions) leads to heterogeneous, toxic and antigenic AGEs and to reactive precursors that are implicated in the pathogenesis of **diabetes**. Pyridoxamine and thiamine

pyrophosphate potently inhibit AGE formation, suggesting that these two compounds may have clinical potential in preventing vascular complications in type 2 **diabetes** and in insulin resistance.

SUMM [0525] Se, and more efficiently Se plus Vitamin E, supplementation in **diabetes** may play a role in controlling oxidative status and unfavorable lipid metabolism in the liver, thereby maintaining favorable fatty acid. . .

SUMM . . . while the exact mechanism is not clear, taurine also inhibits lipid peroxidation and decreases blood triglycerides and LDL-cholesterol levels in **diabetes**.

SUMM [0530] A deficient dietary level of taurine is associated with a variety of pathologies, including type 2 **diabetes**. Since 1981 taurine has been added to infant formulas and parental nutrition solutions in countries around the world and was. . .

SUMM . . . sensitivity, reducing hypercholesterolemia, inhibiting peroxidation of cell membrane components and modulating pericyte and other cell volume instabilities of type 2 **diabetes**. Its ACE inhibitor-like action adds an important dimension in modulating the characteristic hypertension of progressive insulin resistance and type 2 **diabetes**. The cardiac failure seen in later stages of these diseases may benefit from the mild cardiac glycoside-like effect of taurine,. . .

SUMM . . . protecting the pancreatic .beta.-cells from lipid peroxidation, thereby reducing the resulting .beta.-cell dysfunctional apoptosis that can lead to "type 1.5 **diabetes**".

SUMM [0535] Intracellular taurine declines with advancing age and in type 2 **diabetes**. This compounded decrease during both senescence and type 2 **diabetes** exacerbates age-related declines in antioxidant defense systems, Ca.sup.2+ regulation and membrane integrity. The actions of sulfonylurea in K.sup.+ channel blockade,. . . repolarized and is again receptive to sulfonylurea stimulation. However, taurine, carnitine and Mg.sup.2+ are all characteristically deficient in type 2 **diabetes**. This emphasizes the importance of the use of components described in this invention in formulations containing metformin and/or sulfonylurea.

SUMM . . . disorganization and cellular dysfunction or death, all of which are aggravated by taurine deficiency. A number of the complications of **diabetes** are associated with or attributed to osmotic disruption of the cytoarchitecture. These may be lessened if there is adequate intracellular taurine and are worsened if there is a deficiency of taurine, as there often is in **diabetes**.

SUMM . . . that occurs in response to high glucose levels. An increase in TGF-.beta. is implicated in the pathogenesis of glomerulosclerosis in **diabetes**.

SUMM [0546] Approximately 80% of all patients with **diabetes** die of cardiovascular disease. Treatment with sulfonylurea-metformin has been ineffective in altering this dismal prognosis. Progressive insulin resistance, the fundamental defect of type 2 **diabetes** leads to hyperinsulinemia, which is associated with hypertension, atherogenic dyslipidemia, left ventricular hypertrophy, impaired fibrinolysis, visceral obesity, and a sedentary. . . conditions are associated with atherosclerosis and adverse cardiovascular events, the therapeutic effect of sulfonylurea and/or metformin treatment in patients with **diabetes** focuses solely on normalizing glucose levels and may even increase hyperinsulinemia, increasing the risk of cardiovascular events. Metformin and/or sulfonylurea. . .

SUMM . . . destructive mechanisms involved with vascular endothelial damage and is at the root of many long-term complications of insulin resistance and **diabetes**, particularly nephropathy and retinopathy.

SUMM . . . the principal cause of the loss of cell membrane integrity in many pathologic states of vascular and neuronal cells, including

diabetes. Tocopherol preserves SOD, involved in free radical hydrogen peroxide defense.

SUMM [0555] Increased oxidative stress, hypofibrinolysis and insulin resistance are present in obese type 2 **diabetes** patients. High doses of vitamin E (600 mg/day) used alone, may further worsen insulin efficiency and increase fibrinolysis in these. . .

SUMM . . . they increase the effectiveness, efficiency, and safety of combinations of sulfonylurea-metformin in the prevention and treatment of insulin resistance and **diabetes** mellitus and addresses their shortcomings in diabetic macrovascular disease.

SUMM [0563] **Vanadium**

SUMM [0564] Most patients with type 2 **diabetes** mellitus require pharmacotherapy, initially as monotherapy, subsequently in combination. Exogenous insulin is ultimately required in a substantial proportion, reflecting the. . .

SUMM [0565] **Vanadium** increases both hepatic and peripheral insulin sensitivity, thus expanding the activity of combinations of sulfonylurea-metformin. It also activates glycogenesis and. . .

SUMM [0566] **Vanadium** has therapeutic potential in both type 1 and type 2 **diabetes** in doses ranging from 0.083 mmol/d to 0.42 mmol/d. Although **vanadium** has significant biological potential, it has a poor (narrow) therapeutic index. Organic forms of **vanadium**, as opposed to the inorganic sulfate salt, may be safer, more absorbable, and may be able to deliver a therapeutic effect up to 50% greater than the inorganic forms. **Vanadium** has been administered to pregnant women diagnosed with pregnancy-induced **diabetes** without adverse effects upon either the mother or fetus.

SUMM [0567] **Vanadium** is present in a variety of foods that we commonly eat. The daily dietary intake in humans varies from 10 micrograms to 2 mg of elemental **vanadium**, depending on the sources available in various regions. The 100 mg/day often used in treating type 2 **diabetes** is clearly greater than physiological, probably accounting for what is described as a narrow therapeutic index. Utilizing **vanadium** as one element in multicomponent formulations, as defined in this invention, will permit the dosage to be minimized and safety. . .

SUMM [0569] Vanadate (V.sup.5+), an oxidized form of **vanadium**, or vanadyl (V.sup.4+) promote both hepatic and peripheral insulin action by three mechanisms: 1) direct insulin-mimesis; 2) enhancement of insulin sensitivity and 3) prolongation of the insulin biological response. The insulin-mimetic action of these forms of **vanadium** persists after withdrawal of treatment. **Vanadium** treatment of non-diabetic animals lowers plasma insulin levels by reducing insulin demand, and these animals remain normoglycemic. Chronic treatment with **vanadium** has also been shown to result in sustained antidiabetic effects in STZ-diabetic animals long after treatment has ceased. Thus, 13 weeks after withdrawal from **vanadium** administration, treated animals have normalized glucose levels and normal weight gain, and improved basal insulin levels. In addition, near-normal glucose tolerance is found despite an insignificant insulin response. Since **vanadium** accumulates in several tissue sites when pharmacological doses are administered (e.g., bone, kidney), it is possible that stored **vanadium** may be important in maintaining near-normal glucose tolerance, at least in the short-term following withdrawal from treatment.

SUMM . . . 3 weeks of vanadyl sulfate (100 mg/day), both hepatic and peripheral insulin sensitivity appear to improve in insulin-resistant type 2 **diabetes** patients. These effects are sustained for up to 2 weeks after discontinuation of vanadyl sulfate.

SUMM [0572] **Vanadium** has several mechanisms of action in progressive insulin resistance and type 2 **diabetes**:

SUMM [0587] Tolerance does not appear to develop with long term oral administration of **vanadium**, but the safety of chronic **vanadium** treatment beyond five months is not yet established. This may have an impact on the therapeutic use of **vanadium**. To reduce this possibility of chronic use toxicity, the invention describes a pulsing of **vanadium** administration and/or once a day bedtime use to take advantage of the prolonged **vanadium** insulin-mimetic effect following withdrawal of treatment.

SUMM [0590] The relationship between **diabetes**, insulin and Zn.sup.2+ is complex. Functioning as an insulin cofactor, Zn.sup.2+ prevents hyperglycemia by increasing insulin activity at its receptor. . . tend to have low plasma Zn.sup.2+ concentrations and decreased total body Zn.sup.2+. Hyperglycemia, rather than any primary lesion related to **diabetes**, is responsible for increased urinary loss and a decrease in total body Zn.sup.2+, which in turn is in part responsible. . .

SUMM . . . control subjects, a significantly lower Cu, Zn-superoxide dismutase activity is found in both lymphocytes and polymorphonuclear cells of type 1 **diabetes** and type 2 **diabetes** patients. A Zn.sup.2+ deficiency can, therefore, reduce immunoefficiency or aggravate an existing immune deficiency, and contribute to the slow wound. . .

SUMM . . . patients with hypertension or congestive heart failure, but also for the prevention of the progression of renal dysfunction induced by **diabetes** mellitus.

SUMM

. . . 24 to 3000	80 to 1200	
L-Carnitine	90 to 2500	300 to 1000
Choline	15 to 250	50 to 100
Chromium	0.01 to 0.63	0.03 to 0.25
Folate	0.03 to 2.0	0.10 to 0.80
Lipoate	30 to 1500	100 to 600
. . . 15 to 1600	50 to 800	
Tocotrienol	15 to 2000	50 to 800
Ubiquinone	4.5 to 225	15 to 90
Vanadium	7.5 to 375	25 to 150
Vitamin B12	0.001 to 0.010	0.002 to 0.004
Zinc	1.5 to 80	5. . .

DETD . . . of sulfonylurea or metformin pharmaceuticals, and of combined sulfonylurea/metformin pharmaceutical agents, in the prevention and treatment of insulin resistance and **diabetes** mellitus, as an active ingredient for humans. The carefully chosen active ingredients of the invention provide therapeutic levels of a. . . biochemical partnership with these drugs to avoid the development of, or ameliorate, progressive insulin resistance, to retard its progression to **diabetes** mellitus and to ensure an improvement in glucose tolerance, hypertension and obesity associated with type 2 **diabetes**, and a reduction in the morbidity rate. The invention anticipates that diabetic microvascular complications (nephropathy, retinopathy, neuropathy, etc.) as well. . .

DETD [0657] Formulations designed for different aspects of progressive insulin resistance and type 2 **diabetes** processes are illustrated in the specifications and defined in the section on claims. Formulations will be used in appropriate sequencing,. . .

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DETD [0687] Melchior W R, Jaber L A. Metformin: an antihyperglycemic agent for treatment of type II **diabetes**. Ann Pharmacother 1996; 30(2):158-64.

DETD [0697] UKPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 **diabetes** (UKPDS 34). UK Prospective **Diabetes** Study (UKPDS) Group. Lancet 1998; 352(9131):854-865.

DETD [0699] White J, Jr., Campbell R K. Magnesium and **diabetes**: a review. Ann Pharmacother 1993; 27(6):775-80. (the Amer Diab Ass statement)

DETD [0700] Wiernsperger N F. Membrane physiology as a basis for the cellular effects of metformin in insulin resistance and **diabetes**. **Diabetes** Metab 1999; 25(2):110-27.

CLM What is claimed is:

. . . for supporting mitochondrial metabolism as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) choline, (b) ascorbate (c) L-carnitine, (d). . .

. . . membrane integrity for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) D,.alpha.-lipoic acid, (b) ubiquinone, (c) L-arginine,. . .

. . . pancreatic .beta.-cells for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) **chromium**, (b) L-arginine, (c) **vanadium**, (d) zinc, and, (e) metformin.

9. A unit dosage form in accordance with claim 8 in which: (a) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, (b) said L-arginine is in an amount ranging from about 75 mg

to about 3100 mg, (c) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (d) said zinc is in an amount. . . . . specifically for nocturnal use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) melatonin, (b) L-carnitine, (c) ubiquinone, (d). . . . . layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
chromium	40-60%	balance
L-arginine	40-60%	balance
vanadium	40-60%	balance
zinc	40%-60%	balance
metformin	40%-60%	balance

. . . for supporting mitochondrial metabolism as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) choline, (b) ascorbate, (c) L-carnitine, (d). . . . . membrane integrity for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) D,.alpha.-lipoic acid, (b) ubiquinone, (c) L-arginine,. . . . . pancreatic .beta.-cells for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) **chromium**, (b) L-arginine, (c) **vanadium**, (d) zinc, and (e) a sulfonylurea or a sulfonylurea-like compound.

24. A unit dosage form in accordance with claim 23 in which: (a) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (d) said zinc is in an amount. . . . . specifically for nocturnal use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) melatonin, (b) L-carnitine, (c) ubiquinone, (d). . . . . layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
chromium	40-60%	balance
L-arginine	40-60%	balance
vanadium	40-60%	balance
zinc	40%-60%	balance
sulfonylurea or sulfonylurea-like compound	40%-60%	balance

. . . for supporting mitochondrial metabolism as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) choline, (b) ascorbate, (c) L-carnitine, (d). . .

. . . membrane integrity for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) D,.alpha.-lipoic acid, (b) ubiquinone, (c) L-arginine,. . .

. . . pancreatic .beta.-cells for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) **chromium**, (b) L-arginine, (c) **vanadium**, (d) zinc, and, (e) a sulfonylurea (or a sulfonylurea-like)-biguanide complex.

39. A unit dosage form in accordance with claim 38 in which: (a) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (d) said zinc is in an amount. . .

. . . specifically for nocturnal use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) melatonin, (b) L-carnitine, (c) ubiquinone, (d). . .

. . . layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
chromium	40-60%	balance
L-arginine	40-60%	balance
vanadium	40-60%	balance
zinc	40%-60%	balance
sulfonylurea-biguanide	40%-60%	balance

52. A unit dosage form in accordance with claims 7, 22 or 37 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

53. A unit dosage form in accordance with claims 7, 22 or 37 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

. . . treating a patient who requires biguanide therapy for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said biguanide therapy. . .

. . . patient who requires biguanide therapy for the for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said biguanide therapy. . .

. . . patient who requires biguanide therapy for the for the prevention, management, and clinical amelioration of insulin resistance and type 2

diabetes and conditions giving rise thereto, to reduce undesirable physiological side effects, for the preservation and functional maintenance of insulin receptors. . . of said biguanide therapy, said method comprising administering to said patient a unit dosage form comprising as active ingredients: (a) **chromium**, (b) L-arginine, (c) **vanadium**, (d) zinc, and (e) metformin.

64. A method in accordance with claim 63 in which: (a) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (d) said zinc is in an amount. . . . . treating a patient who requires nocturnal biguanide for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and to enhance the therapeutic effectiveness of said biguanide. . . . . immediate-release layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
chromium	40-60%	balance
L-arginine	40-60%	balance
vanadium	40-60%	balance
zinc	40%-60%	balance
metformin	40%-60%	balance

77. A method in accordance with claim 62 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

80. A method in accordance with claim 62 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

. . . treating a patient who requires sulfonylurea therapy for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said sulfonylurea therapy. . . . . patient who requires sulfonylurea therapy for the for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said sulfonylurea therapy. . . . . patient who requires sulfonylurea therapy for the for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said sulfonylurea therapy. . . receptors and pancreatic .beta.-cells, said method comprising administering to said patient a unit dosage form comprising as active ingredients: (a) **chromium**, (b) L-arginine, (c) **vanadium**, (d) zinc, and (e) a sulfonylurea or a sulfonylurea-like compound.

89. A method in accordance with claim 88 in which: (a) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **vanadium** is in an amount ranging

from about 7.5 mg to about 375 mg, (d) said zinc is in an amount. . . . . specifically for nocturnal use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) melatonin, (b) L-carnitine, (c) ubiquinone, (d). . . . . immediate-release layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
chromium	40-60%	balance
L-arginine	40-60%	balance
vanadium	40-60%	balance
zinc	40%-60%	balance
sulfonylurea or sulfonylurea-like compound	40%-60%	balance

102. A method in accordance with claim 87 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

105. A method in accordance with claim 87 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

. . . requires sulfonylurea (or a sulfonylurea-like)-biguanide complex therapy for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said combined sulfonylurea-biguanide. . . . . (or a sulfonylurea-like)-biguanide complex therapy for the for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said combined sulfonylurea-biguanide. . . . . (or a sulfonylurea-like)-biguanide complex therapy for the for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness of said combined sulfonylurea-biguanide. . . receptors and pancreatic .beta.-cells, said method comprising administering to said patient a unit dosage form comprising as active ingredients: (a) **chromium**, (b) L-arginine, (c) **vanadium**, (d) zinc, and, (e) a sulfonylurea (or sulfonylurea-like)-biguanide complex.

114. A method in accordance with claim 113 in which: (a) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (d) said zinc is in an amount. . . . . specifically for nocturnal use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) melatonin, (b) L-carnitine, (c) ubiquinone, (d). . . . . sustained-release layer in the following approximate proportions

expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
chromium	40-60%	balance
L-arginine	40-60%	balance
vanadium	40-60%	balance
zinc	40%-60%	balance
sulfonylurea-biguanide	40%-60%	balance

127. A method in accordance with claim 112 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

130. A method in accordance with claim 112 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

L2 ANSWER 2 OF 4 USPATFULL
AN 2003:112605 USPATFULL
TI Formulations for the prevention and treatment of insulin resistance and type 2 **diabetes** mellitus
IN Richardson, Kenneth T., Anchorage, AK, UNITED STATES
Pearson, Don C., Lakewood, WA, UNITED STATES
PA ChronoRX LLC, Anchorage, AK (U.S. corporation)
PI US 2003077335 A1 20030424
AI US 2001-33730 A1 20011102 (10)
PRAI US 2000-245471P 20001103 (60)
US 2000-245950P 20001103 (60)
US 2000-256033P 20001213 (60)
DT Utility
FS APPLICATION
LREP TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
CLMN Number of Claims: 104
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4450
TI Formulations for the prevention and treatment of insulin resistance and type 2 **diabetes** mellitus
AB . . . increasing the effectiveness, efficiency and safety of biguanides (metformin) and/or sulfonylureas in the prevention and treatment of insulin resistance and **diabetes** mellitus, alone or in combination, as a nutrient for humans. The carefully chosen active ingredients of the invention are designed in a modular fashion to prevent and rectify adverse events associated with insulin resistance syndrome and **diabetes** mellitus, and with the clinical use of biguanides (metformin) and/or the sulfonylureas. These modules are: (1) Mitochondrial Metabolic Group, (2). . . will broaden the clinical usefulness of these drugs. The invention will retard the progression of insulin resistance to type 2 **diabetes**, and reduce the serious microvascular and macrovascular complications commonly associated with insulin resistance syndrome and **diabetes** mellitus.
SUMM . . . of the biguanide metformin, the sulfonylureas or combinations of sulfonylurea-metformin, in the pharmacological treatment of insulin resistance and type 2 **diabetes** mellitus.

09/156,102 6376548

SUMM [0005] Insulin resistance and non-insulin-dependent **diabetes** are prevalent in up to 35% of the population depending upon the age and nature of the subset. In the United States alone, 16 million people have type 2 **diabetes** and 13 million have impaired glucose tolerance. In fact type 2 **diabetes** has reached epidemic proportions worldwide. By 2025, an estimated 300 million people will have **diabetes**, most of whom will inhabit China, India, and the United States. Because of an aging and increasingly sedentary, obese population. . . unhealthy diets, insulin resistance is also increasing alarmingly (it is already two to three times more prevalent than type 2 **diabetes**). This apparent increase in the prevalence of insulin resistance and type 2 **diabetes** occurs in all ethnic populations, but especially in those that have migrated from their native lands to more urbanized and. . .

SUMM [0006] Insulin resistance and type 2 **diabetes** exist not merely as part of the aging process, but also as a process that advances aging. **Diabetes** affects metabolism in totality: carbohydrate, lipid and protein. Its causes and its management are very, very complex and strikingly nonlinear.

SUMM [0007] Patients with **diabetes** of all types have considerable morbidity and mortality from microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (heart attacks, stroke, peripheral vascular. . . leading cause of blindness in the United States) and/or macular edema occur in about 50% of patients with type 2 **diabetes**, as do peripheral and/or autonomic neuropathy. b) The incidence of diabetic renal disease is 10% to 50% depending on ethnicity.. . . Diabetics have heart attacks, strokes and peripheral vascular disease at about triple the rate of non-diabetics. The cost of treating **diabetes** and its complications exceeds $100 billion annually. In addition to these dreadful data, insulin resistance (a prelude to type 2 **diabetes** in about 50% of those effected) with its associated hypertension, coagulopathy, dyslipidemia and obesity substantially adds to these morbidity, mortality. . .

SUMM [0008] There are two clinical forms of **diabetes**, each with a different pathogenesis: type 1, insulin dependent **diabetes** mellitus and type 2, non-insulin dependent **diabetes** mellitus. The latter represents 90% of all diabetics. In type 2 **diabetes** , cellular resistance to the functional effectiveness of insulin results in above normal levels of insulin secretion. When this compensatory increase. . . increases further, blood sugar rises, lipid and protein metabolism are disturbed, and the insidious processes of vascular complications of long-term **diabetes** begin.

SUMM [0009] The fasting hyperglycemia of type 2 **diabetes** exists in the presence of hyperinsulinemia; this reflects the presence of insulin resistance in the liver with resultant glycogenolysis and. . .

SUMM [0012] Free radical generation and induced nitric oxide synthase (iNOS) production secondary to the hyperglycemia of type 2 **diabetes** can lead to pancreatic .beta.-cell destruction, and the production of diagnostic enzymatic indicators characteristic of type 1 **diabetes**. This fact has introduced the term "type 1.5 **diabetes**". In this scenario, .beta.-cells are not only "exhausted" by the progression of pathology from insulin resistance to type 2 **diabetes**, but may also undergo destruction induced by chronic hyperglycemia.

SUMM [0013] Hypertension, dyslipidemia, coagulopathy, obesity and development of type 2 **diabetes**--all of which may follow chronic insulin resistance--are largely preventable, as are the eventual diabetic micro- and macrovascular complications. In those patients with insulin resistance who do progress to type 2 **diabetes**, successful treatment requires maintenance of blood glucose at a normal preprandial level (or at a postprandial level below 180 dl). . .

SUMM . . . Microproteinuria, due to its inadequacy in the glomerular

basement membrane, is one of the earliest, most consistent early signs of **diabetes**, and diabetic nephropathy is invariably associated with progressive proteinuria. Reductions of heparan sulfate in the basement membrane of retinal and. . .

SUMM . . . to many disorders associated with aging, i.e., hypertension, obesity, atherosclerosis, lipid abnormalities, coagulopathies and chronic metabolic perturbations including type 2 **diabetes**.

SUMM [0016] Although insulin resistance and type 2 **diabetes** each have an inherited pathogenic component, they both are substantially influenced by inappropriate diet and inadequate exercise.

SUMM [0017] In aging, as in **diabetes**, elevated circulating glucose reacts nonenzymatically with proteins and nucleic acids to form products that: 1) disturb the functionality of the. . .

SUMM [0018] The ingestion of sugars, fats, and sodium have been linked to insulin resistance, while caloric restriction, exercise, ingestion of **chromium**, **vanadium**, magnesium, and certain antioxidants are associated with greater insulin sensitivity. Lifespan may favorably be affected, and the incidence of many chronic disorders commonly associated both with aging and with **diabetes** can be reduced, by manipulating the diet and its influence upon the glucose/insulin system.

SUMM **Diabetes**--Pertinent Anatomy and Physiology of Glucose Metabolism

SUMM . . . response) of .beta.-cells to the small amount of insulin that is present may ultimately lead to clinically overt type 2 **diabetes** and its more serious, often devastating complications. (See below.)

SUMM . . . into cells, insulin stimulates cellular uptake of potassium and ascorbate. Thus, when combined with the usually existing Mg.sup.2+ inadequacy of **diabetes**, insulin deficiencies exaggerate or cause hypertension, reductions in available circulating ascorbate and the "tissue scurvy" commonly associated with type 2 **diabetes**. This ascorbate deficit in turn contributes to the hypertension of insulin resistance and **diabetes** by reducing available BH4, the cofactor essential for endothelial nitric-oxide synthase (eNOS) activity, which maintains physiological vasodilatation.

SUMM . . . to the interplay of two or more signaling processes that result in reciprocal modulation. In the treatment of type 2 **diabetes**, the ability of caveolae to sequester molecules provides a target for influencing both imported and locally produced molecules in the. . .

SUMM . . . in glucose transport and GLUT4 vesicle translocation. It should be noted here that the antihyperglycemic effect of the trace element **vanadium** may in part be due to direct activation of the insulin receptor and in part to a prolongation of the. . .

SUMM . . . Mg.sup.2+ as a cofactor. Mg.sup.2+ deficiency is sufficiently common in diabetics that its oral supplementation is recommended by the American **Diabetes** Association for diabetics with normal renal function.

SUMM [0043] Pancreatic .beta.-cell apoptosis is responsible for irreversible progression toward insulin dependence in type 2 **diabetes**.

SUMM . . . in these processes. The inadequacy or lack of such modulation at multiple points may eventually lead to overt type 2 **diabetes** itself. The identification and influence of these modulation points represent therapeutic opportunities and underly the rationale of this invention.

SUMM [0051] Although circulating insulin levels are frequently elevated early in type 2 **diabetes**, a deficiency of intracellular insulin and increased cellular resistance to many of insulin's actions simultaneously occur: there is resistance to. . .

SUMM . . . adipocytes of obese individuals, and that this TNF-.alpha. is a principal contributor to insulin resistance and its subsequent type 2 **diabetes** of obesity. TNF-.alpha. is an important regulator of

the processes of apoptosis and thus modulates the volume of tumor, adipose. . .

SUMM [0055] It is clear that the process governing both insulin resistance and type 2 **diabetes** is diagrammically syncytial. It is not a linear, straightforward process that lends itself to a single treatment modality. Neither disease. . .

SUMM Aging and **Diabetes** Mellitus

SUMM . . . insulin at its receptor site and a decreased response by the pancreatic .beta.-cells to glucose levels. In aging, similar to **diabetes**, the elevated circulating glucose secondary to increasing insulin resistance reacts nonenzymatically with proteins and nucleic acids to form products that. . . from elevated free radical formation resulting from the autooxidation of glucose. Augmented free radical formation and lipid peroxidation, common in **diabetes** mellitus, are associated with the "premature aging" of diabetic patients. Long term, excessive ingestion of sugars, fats and sodium have been linked to decreased insulin sensitivity, while caloric restriction, exercise, ingestion of **chromium**, **vanadium**, Mg.sup.2+, certain free radical scavengers and nuclear factor kappa B (NFkappaB) inhibitors are associated with greater insulin sensitivity. Thus, manipulation. . . the glucose/insulin system may favorably affect lifespan and reduce the incidence of the microvascular and macrovascular complications of type 2 **diabetes**.

SUMM [0057] The earliest microvascular lesion of **diabetes** is a variable thickness of the basement membrane. A healthy basement membrane provides vascular stability and importantly, a permeability barrier.. . . acid, n-acetylcysteine (NAC) and possibly taurine may contribute to the adequacy of this necessary negativity of the cell membrane. In **diabetes** both the basement membrane thickness and heparan sulfate levels are decreased. As a result, vessel permeability is increased. Increased vessel permeability is the most notable initial microvascular complication in **diabetes**.

SUMM [0058] Early in **diabetes** there are additional abnormal microvascular (arteriolar and capillary) dysfunctions; intraluminal pressure and flow are both increased. These, plus the increased. . .

SUMM [0061] 2. Diabetic nephropathy is common in type 2 **diabetes**. Risk of death is increased 100 fold.

SUMM [0074] Although **diabetes** mellitus and insulin resistance are progressive, complex and frequently unpredictable processes with many points of potential instability, the latter are identifiable. To have any long-term chance of favorably influencing the cellular pathophysiology of insulin resistance and type 2 **diabetes**, any clinical approach must involve not only the coordination of life style modification, but also utilize finely calibrated combinations of. . .

SUMM [0075] Therefore it is useful to consider, in turn, the pathologic states caused by insulin resistance and type 2 **diabetes**, the underlying molecular biologic defects or deficiencies, the existing modalities for favorably modulating these and the complementary, beneficial interactions of. . .

SUMM [0076] A. Pathologic States Caused by or Worsened by Insulin Resistance and/or Type 2 **Diabetes**

SUMM [0093] B. Cellular Physiological and Molecular Biological Disturbances in Insulin Resistance and/or Type 2 **Diabetes**

SUMM . . . are currently available: biguanides (e.g., metformin), sulfonylureas (e.g., tolbutamide, glyburide, glipizide and others), .alpha.-glucosidase inhibitors (e.g., acarbose and miglitol) and **thiazolidinediones** (e.g., troglitazone and rosiglitazone), each of these has a different mode and site of action.

SUMM . . . use of both (i.e., a combination of sulfonylurea and biguanide) for treatment of progressive insulin resistance and type two **diabetes**.

SUMM [0138] The principle of long-term maintenance of glucose control applies

to both progressive insulin resistance and type 2 **diabetes**. The treatment strategies while similar, are somewhat different. Progressive insulin resistance has as its central abnormality hyperinsulinemia. The latter persists as the disease progresses to type 2 **diabetes** with its central abnormality, hyperglycemia. In each case the process is nonlinear and its pharmacological modulation is complex.

SUMM . . . the associated defects in insulin secretion. This not only has direct implications for adequate classification and treatment of type 2 **diabetes** in the elderly, but also for understanding the autoimmune/inflammatory mechanisms involved in the pathogenesis of hyperglycemia.

SUMM . . . .beta.-cell apoptosis, this invention will enhance the effectiveness of sulfonylurea therapy by stopping or slowing the progression of type 2 **diabetes** toward this stage of progressive autoimmune/inflammatory .beta.-cell destruction--sometimes referred to as "type 1.5" **diabetes**.

SUMM . . . unsatisfactory. It is the intention of this invention to extend the duration of effect of sulfonylurea treatment of type 2 **diabetes** by delaying the onset, and slowing the progression, of .beta.-cell dysfunction and inappropriate .beta.-cell apoptosis.

SUMM [0161] Regarding the benefit of intensive therapy with sulfonylureas (chlorpropamide, glibenclamide) or with insulin in type 2 **diabetes**, the UKPDS interpreted their data to indicate that ". . . intensive blood glucose control by either of the sulphonylureas. . .

SUMM [0162] Management of patients with progressive insulin resistance and type 2 **diabetes** should focus on decreasing the excess macrovascular disease with which these are associated, as well as preventing or minimizing microvascular. . . However, this requires the concomitant management of the cardiovascular risk factors of the insulin resistance syndrome associated with type 2 **diabetes**: e.g., a reduction of the macrovascular-disease-promoting sulfonylurea side effects (e.g., carnitine depletion) and/or (possibly) a reduction of metformin-induced hyperhomocysteinemia.

SUMM [0166] Type 2 **diabetes** mellitus is part of a complicated metabolic-cardiovascular pathophysiologic cluster alternately referred to as the insulin resistance syndrome, Reaven's syndrome, the metabolic syndrome or syndrome X. Since the macrovascular coronary artery disease associated with insulin resistance and type 2 **diabetes** is the major cause of death in the latter, it is desirable that any hypoglycemic agent favorably influences known cardiovascular. . .

SUMM . . . independent of their hypoglycemic properties. These additional actions may be useful in preventing or attenuating the long-term vascular complications of **diabetes**, e.g., diabetic retinopathy. While the favorable effect of reducing platelet aggregation seems established, a disturbing recent study shows an increase. . .

SUMM . . . in the homeostasis of other amino acids for which deficiencies should be avoided in progressive insulin resistance and type 2 **diabetes**, e.g., taurine and L-arginine. Given these renal effects of the sulfonylureas, it is not surprising that there macrovascular benefits are. . .

SUMM [0185] The controversial results of the University Group **Diabetes** Program study (1970) suggested that sulfonylureas might exacerbate coronary artery disease in patients with type 2 **diabetes**. Subsequent clinical trials have not demonstrated these increased cardiac mortality rates in diabetic patients actually treated with sulfonylureas. In fact, the UKPDS found no increased incidence of coronary artery disease in those patients with type 2 **diabetes** , who were assigned to intensive therapy with sulfonylureas, when compared with patients receiving diet therapy. There is no published data to support an advantage of any one sulfonylurea with respect to coronary artery disease. An American **Diabetes** Associations

policy statement opposes any formal restrictions based on the interpretations of the University Group **Diabetes** Program findings.

SUMM . . . safety improved and the scope of their beneficial effects broadened in progressive insulin resistance, insulin resistance syndrome and type 2 **diabetes** by formulations of this invention.

SUMM [0189] A.6. Adjunctive use of the Invention for the Prevention and Treatment of Insulin Resistance Syndrome and Type 2 **Diabetes**

SUMM . . . As illustrated by the foregoing list of cellular physiological and molecular biological disturbances, both insulin resistance syndrome and type 2 **diabetes** are progressive complex, dynamic metabolic system failures with potential instability at many points. Its genesis is in part related to. . . known to be detrimental to persons with the potential for developing (or who already have) insulin resistance or type 2 **diabetes**. This physiologic modulation is achieved by the formulations of this invention and is the basis for their improvement in the. . .

SUMM [0191] As an individual progresses toward and into type 2 **diabetes**, an increasing number of specific complementary biomolecules, biofactors and trace elements are necessary to compliment sulfonylureas, as shown in the. . .

SUMM . . . form for increasing the effectiveness, efficiency and safety of sulfonylureas in prevention and treatment of insulin resistance and/or type 2 **diabetes**. The preparation contains specific, sometimes unique, therapeutic biomolecules, biofactors and trace elements selected because of their particular and critical, combinational. . .

SUMM . . . of the invention will be effective in preventing the development or slowing the progression of insulin resistance and type 2 **diabetes**. This may delay the time when a sulfonylurea is required and so reduce the adverse effects that accumulate with prolonged. . .

SUMM [0194] In the United States alone, 16 million people have type 2 **diabetes** and a substantial multiple, perhaps 4.times. to 5.times., are insulin resistant--at least one-half of these are undiagnosed. Type 2 **diabetes** is preceded by a long period of insulin resistance, impaired glucose tolerance and a reversible metabolic state associated with an. . .

SUMM [0195] Susceptibility to type 2 **diabetes** requires both genetic (most likely polygenic) and acquired factors. Its continuing pathogenesis involves an interplay of progressive cellular insulin resistance and pancreatic .beta.-cell failure. Any ideal treatment of type 2 **diabetes** must reduce insulin resistance and .beta.-cell dysfunction in a majority of treated patients and prevent, delay, or reverse the long-term. . .

SUMM . . . action in order to provide for better sulfonylurea management of the insulin resistance syndrome, more efficient prevention of type 2 **diabetes**, better management of type 2 **diabetes** and for prevention of long-term macrovascular and microvascular complications.

SUMM [0198] The complexity of type 2 **diabetes** pathophysiology provides the opportunity to expand sulfonylureas' clinical usefulness by the administration of complementary, novel combinations of biomolecules, biofactors and. . .

SUMM [0222] This invention provides adjunct formulations to enhance treatment of progressive insulin resistance and type 2 **diabetes** with a sulfonylurea. This invention addresses sulfonylurea-induced mitochondrial malfunction and the failure of sulfonylurea to prevent diabetic macrovascular disease. It. . .

SUMM [0227] Metformin has a unique mechanism of action and controls glycemia in both obese and normal-weight, type 2 **diabetes** patients without inducing hypoglycemia, insulin stimulation or hyperinsulinemia. It prevents the desensitization of human pancreatic islets usually induced by hyperglycemia. . .

SUMM . . . eliminated primarily by renal filtration and secretion and has a half-life of approximately 6 hours in patients with type 2 **diabetes**; its half-life is prolonged in patients with renal impairment. It has no effect in the absence of insulin. Metformin is as effective as the sulfonylureas in treating patients with type 2 **diabetes**, but has a more prominent postprandial effect than either the sulfonylureas or insulin. It is therefore most useful in managing. . .

SUMM [0232] Except perhaps for its appearance in aging, insulin resistance and type 2 **diabetes** do not usually occur in isolation, but as part of the complex metabolic-cardiovascular `Syndrome X`, mentioned previously. Hyperinsulinemia and hyperglycemia. . . avoided. Long-term prospective studies have shown that treatment of hypertension and dyslipidemia reduces cardiac events in patients with type 2 **diabetes**. As an example, the United Kingdom Prospective **Diabetes** Study (UKPDS) showed that improved control of blood pressure reduced not only macrovascular complications (heart attacks, strokes, and death), but. . . to their improvement. Because obesity and physical inactivity are global risk factors for coronary artery disease as well as for **diabetes**, the need for weight loss and exercise must be stressed when **diabetes** initially is diagnosed, and must be reinforced throughout the natural history of the disease. However, modification of these may not. . .

SUMM . . . hyperinsulinemia, metformin improves levels of plasminogen activator inhibitor (PAI-1) and thus improves fibrinolysis in insulin resistance patients with or without **diabetes**. Weight gain does not occur in patients with type 2 **diabetes** who receive metformin; in fact, most studies show modest weight loss (2 to 3 kg) during the first 6 months. . .

SUMM . . . various elements of the insulin resistance syndrome help define its usefulness in the treatment of insulin resistance and type 2 **diabetes**. These useful effects are enhanced when metformin is combined with components of this invention. The latter increase its effectiveness and. . .

SUMM [0238] Unquestionably the UKPDS established that type 2 **diabetes** is a progressive disorder. Ideally, treatment with metformin (or a sulfonylurea, or insulin) would halt the progressive deterioration of glycemic. . . in glycemic control is relentless. In the UKPDS, this decline was related to deterioration of .beta.-cell function. The University Group **Diabetes** Program study similarly confirmed the progressive nature of type 2 **diabetes**. These important studies emphasize the need for constant reassessment of patients with insulin resistance and/or **diabetes**, and for appropriate adjustment of the therapeutic regimen in order to avoid hyperinsulinemia, deterioration or apoptosis of .beta.-cells and progressive. . .

SUMM . . . reducing the risks associated with specific abnormalities of several conditions and functions frequently associated with insulin resistance and/or type 2 **diabetes**. These include, among others, dysfunctional vascular endothelium, inappropriate apoptosis, undesirable platelet agglutination, inadequate maintenance of cell volume, dyslipedemia, hyperhomocysteinemia, .beta.-cell. . .

SUMM [0248] B.4. Adjunctive use of the Invention for the Prevention and Treatment of Insulin Resistance Syndrome and Type 2 **Diabetes**

SUMM [0249] As an individual progresses from often-covert insulin resistance toward and into type 2 **diabetes**, and has a corresponding need for drug therapy, metformin is often the drug of choice. However, because of limitations upon. . .

SUMM . . . forms for increasing the effectiveness, efficiency and safety of metformin therapy in the treatment of insulin resistance and/or type 2 **diabetes**. The preparation contains specific, sometimes unique, therapeutic biomolecules, biofactors and trace elements selected

because of their particular and critical, combinational. . .

SUMM . . . action in order to provide for better metformin management of the insulin resistance syndrome, more efficient prevention of type 2 **diabetes**, better management of type 2 **diabetes** and for prevention of long-term macrovascular and microvascular complications.

SUMM [0266] Preventing progression from type 2 to "type 1.5" **diabetes** .

SUMM . . . to the clinical use of metformin toward the end of enhancing the treatment of progressive insulin resistance and type 2 **diabetes**. By these various means, the invention will increase the number of patients who will benefit from metformin therapy.

SUMM . . . to provide adjunctive support for a wide spectrum of patients who are at risk of insulin resistance and type 2 **diabetes**, including those who do not require either metformin or a sulfonylurea, those who are prescribed one or the other, and. . .

SUMM . . . carnitine renal loss) tend to normalize the mitochondrial fuel supply. Taurine, often low in progressive insulin resistance and type 2 **diabetes**, is required to move Ca.sup.2+ into the mitochondria to signal ATP production. Magnesium is also necessary in the modulation of. . .

SUMM . . . spiral of, vascular degradation, local hypoxia, thrombogenesis and atrophy/apoptosis causing the macrovascular complications of progressive insulin resistance and type 2 **diabetes**.

SUMM . . . intracellular defense against free radicals generated by mitochondrial metabolism and excess free radicals secondary to hyperglycemia. It becomes depleted in **diabetes**. Metformin increases available GSH in both diabetics and non-diabetics, indicating that it has some antioxidant activity that is independent of,. . .

SUMM [0290] Tetrahydrobiopterin (BH4) is an essential cofactor for nitric oxide synthase. In low concentrations of BH4, as is common in **diabetes**, nitric oxide synthase produces less constitutive NO and, correspondingly, larger quantities of the superoxide anion and hydrogen peroxide.

SUMM [0291] Excessive pancreatic .beta.-cell apoptosis is responsible for the irreversible progression toward insulin dependence found in type 2 **diabetes**. The integrity of the mitochondrial membrane is essential for preventing .beta.-cell dysfunctional apoptosis. The components of this group will inhibit. . .

SUMM [0293] Nocturnal occurrences of myocardial ischemia/reperfusion events is common in progressive insulin resistance and type 2 **diabetes** , and the post-infarction mortality rate in these patients is double that of non-diabetics. Bedtime adjunctive therapy, as defined in this. . .

SUMM [0294] The increased incidence of nocturnal myocardial ischemia and arrhythmias in progressive insulin resistance and type 2 **diabetes** relates to: (1) hypertension, (2) a blunted nocturnal fall in blood pressure, (3) hypoxemia induced by sleep apnea, (4) autonomic neuropathy, and (5) thrombogenesis. These are often interrelated. For example: in hypertension, sleep apnea syndrome and **diabetes** the normal nocturnal fall in blood pressure is absent or reversed. As another example: progressive insulin resistance causes hypertension and. . .

SUMM . . . (4) restoring physiologic fatty acid oxidation, and (5) reducing sleep apnea.

IV INSULIN ALTERNATIVE GROUP
Dosages in Milligrams

	Preferred		Most Preferred	
Vanadium	7.5	to 375	25	to 150
L-Arginine	75	to 3125	250	to 1250

Chromium	0.01	to 0.63	0.03	to 0.25
Zinc	1.5	to 125	5	to 50

SUMM [0299] **Vanadium** mimics insulin intracellularly and prolongs insulin action. It increases both hepatic and peripheral insulin sensitivity, and activates glycogenesis, decreasing hyperglycemia. **Vanadium** preserves pancreatic .beta.-cells, and decreases diabetic hyperphagia, thereby improving both the safety and effectiveness of sulfonylurea and metformin.

SUMM [0300] **Chromium**, often deficient in **diabetes**, is a cofactor for insulin, increasing its binding to the insulin receptor and reducing insulin resistance. It increases the number. . .

SUMM . . . invention will reduce sulfonylurea and/or metformin requirements and will prevent or delay the need for injectable insulin in type 2 **diabetes**.

SUMM [0304] The molecular complexes of this invention address various aspects of insulin resistance and type 2 **diabetes** such as 1) mitochondrial metabolism, 2) mitochondrial membrane integrity, 3) plasma membrane integrity, 4) adverse cytokine cascades, 5) dysfunctional .beta.-cell. . .

SUMM . . . used to increase the effectiveness, efficiency and safety of metformin in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus. They have the following formulae:

SUMM . . . used to increase the effectiveness, efficiency and safety of metformin in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus. They have the following formulae:

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SUMM . . . used to increase the effectiveness, efficiency and safety of metformin in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus. They have the following formulae:

SUMM . . . used to increase the effectiveness, efficiency and safety of metformin in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus.

EXAMPLE

TOCOTRIENOL NICOTINATE

Ranges in milligrams per day	Including Excipients Compound	Tocotrienol	Nicotinate
Preferred	61	34	10
to	1844	1024	293
Most Preferred	307. . .		

SUMM . . . used to increase the effectiveness, efficiency and safety of metformin in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus.

EXAMPLE

D, .alpha.-TOCOPHEROL NICOTINATE

Ranges in milligrams per day	Including Excipients Compound	Tocopherol	Nicotinate
Preferred	61	34	10
to	1844	1024	293
Most Preferred. . .			

SUMM . . . used to increase the effectiveness, efficiency and safety of

metformin in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus.

SUMM . . . used to increase the effectiveness, efficiency and safety of metformin in the prevention and treatment of progressive insulin resistance and **diabetes** mellitus.

SUMM . . . used as adjuncts to pharmaceutical combinations of sulfonylurea and/or metformin in the treatment of progressive insulin resistance and type 2 **diabetes**. The preparation contains specific, sometimes unique, therapeutic biomolecules, biofactors and trace elements selected because of their particular and critical, combinational. . .

SUMM [0380] Type 2 **diabetes** is preceded by a long period of impaired glucose tolerance and a reversible metabolic state associated with an increasing prevalence. . . the time of diagnosis, long-term complications have already developed in almost one fourth of these patients. Susceptibility to type 2 **diabetes** requires both genetic (most likely polygenic) and acquired factors. Its continuing pathogenesis involves interplay between progressive cellular insulin resistance and pancreatic .beta.-cell failure. Any ideal treatment of type 2 **diabetes** must reduce insulin resistance and .beta.-cell dysfunction in a majority of treated patients and, in addition, prevent, delay, or reverse. . .

SUMM [0384] The complexity of progressive insulin resistance and type 2 **diabetes** pathophysiology, and the nature of the effect of either or both sulfonylurea and of metformin on the disease process, provides. . . biomolecules, biofactors and trace elements, many of which are deficient or functionally inadequate in progressive insulin resistance and type 2 **diabetes**, and which are inadequately moderated or worsened by sulfonylurea and/or metformin treatment, the clinical usefulness of the latter will be. . .

SUMM . . . variety of reasons, many of the components are deficient in persons with insulin resistance and in diabetic patients. Mg.sup.2+, ascorbate, **chromium** and certain amino acids (viz., carnitine, taurine) are important examples of such diabetic deficiencies, either because of inadequate intake or. . .

SUMM [0387] L-arginine is usually limited in insulin resistance syndrome and type 2 **diabetes**; an insufficiency that can be overcome by dietary supplementation.

SUMM . . . and thrombosis, and in improving the dynamic and rheological vascular responses in patients with insulin resistance syndrome and/or type 2 **diabetes**.

SUMM . . . L-arginine inhibits lipid peroxidation, additionally protecting the endothelium and reducing long-term microangiopathic complications in insulin resistance syndrome and type 2 **diabetes**.

SUMM . . . administered it increases the effectiveness, efficiency, and safety of combined sulfonylurea-metformin in the prevention and treatment of insulin resistance and **diabetes** mellitus.

SUMM [0396] Diabetics have at least 30% lower circulating ascorbic acid concentrations than people without **diabetes** mellitus. The cellular uptake and cellular level of vitamin C (ascorbic acid, AA) is promoted by insulin and reduced in. . .

SUMM . . . derived directly from inadequate carnitine, the symptoms of weakness and fatigue often seen in progressive insulin resistance and type 2 **diabetes** may relate to carnitine deficient mitochondrial dysfunction, indirectly due to inadequate cytosolic AA.

SUMM . . . generation of reactive oxygen species (ROS) is high and in which ROS production greatly multiplies during pathological processes such as **diabetes**. Normally ROS are effectively protected against by the high capacity of inherent antioxidative systems: enzymes and water- or lipid-soluble low. . .

SUMM . . . from the autooxidation of glucose, hyperglycemia induces oxidative free radical stress. AA has been shown to be highly consumed in **diabetes**, presumably through free radical scavenging. If a

continuous supply of AA is available, it indirectly maintains appropriate levels of other. . .

SUMM . . . to L-arginine in lessening endothelial dysfunction by normalizing constitutive NO production in patients with insulin resistance syndrome and/or type 2 **diabetes**. This action of AA improves impaired acetylcholine-induced vasodilation by a mechanism linked to NO formation. AA selectively restores impaired endothelium-dependent vasodilation even in patients with insulin-dependent **diabetes** mellitus

SUMM . . . to causing oxidative stress, hyperglycemia--via glycation of proteins--generates Maillard products that cross-link. These advanced glycation products occur in vivo in **diabetes** mellitus as well as in aging. Activation of the polyol (sorbitol) pathway leads to such nonenzymatic protein glycation that causes. . .

SUMM . . . reducing agents and is an essential cofactor for the enzymatic activity of eNOS. Suboptimal concentration of BH4, as occurs in **diabetes**, reduces formation of NO and "uncouples" eNOS leading to an eNOS-mediated reduction of oxygen, the formation of superoxide anions and. . .

SUMM . . . when L-arginine, is decreased. Thus, eNOS may become a direct source of reactive oxygen species under pathological conditions such as **diabetes**, when either or both may be lacking. Because NO reacts with the superoxide anion and hydrogen peroxide to form peroxynitrite,. . .

SUMM . . . improved by concomitant oral treatment with BH4: Further evidence that endothelial function--for good or ill--in insulin resistance and Type II **diabetes** is modulated by the availability of BH4

SUMM [0412] Carnitine levels are reduced in **diabetes**, and are further decreased by sulfonylurea treatment.

SUMM . . . fuel; however, glucose may not provide sufficient energy for normal cardiac function, especially in progressive insulin resistance and type 2 **diabetes**. This can lead to severe cardiac arrhythmias, cardiac arrest and death. In addition, the excessive exposure of tissues to fatty. . .

SUMM [0415] As stated, carnitine is deficient in type 2 **diabetes**, and further depleted by sulfonylurea treatment. It is surprising that this important adverse effect--sulfonylurea-induced carnitine deficiency--is seldom referred to. This. . . considers that a major disappointment of sulfonylurea therapy is that it fails to prevent the macrovascular complications of type 2 **diabetes**, presumably, in part because of its adverse effect on carnitine homoeostasis.

SUMM . . . thereby inducing the macrovascular complications associated with carnitine deficiency, which are the same as the macrovascular complications of type 2 **diabetes**: heart attacks, stroke and peripheral vascular disease. Additionally, the reperfusion injury that occurs after a macrovascular ischemic event is worse. . .

SUMM [0418] Serious results from heart attacks, the leading cause of death in type 2 **diabetes**, can be divided into cardiomyopathy, if the area of damage is sufficiently large that the heart can no longer function. . .

SUMM . . . of hepatic fatty acid oxidation by carnitine has considerable clinical potential in patients with both insulin resistance and type 2 **diabetes** although this same activity also tends to enhance hepatic gluconeogenesis, limiting its usefulness to some extent. However, as an adjunct. . .

SUMM . . . carnitine is of enormous physiologic importance, and its deficiency in pathologic states such as progressive insulin resistance and type 2 **diabetes** worsens the outlook. Carnitine is safe and, except for a tendency to increase hepatic gluconeogenesis, it has no side effects. . .

SUMM . . . adjunct, it increases sulfonylurea-metformin effectiveness,

efficiency, and safety in the prevention and treatment of progressive insulin resistance and type 2 **diabetes**, reduces the cardiovascular risks associated with these diseases and reduces adverse side effects which arise from the combined use of. . .

SUMM . . . by transferring one of its methyl groups to homocysteine to form methionine, thereby lessening the threat of homocysteine-induced thrombosis in **diabetes**.

SUMM **Chromium**

SUMM [0430] There is a dietary deficiency of **Chromium** (Cr) in more than one-half of the USA population.

SUMM . . . fat metabolism. Insufficient dietary Cr has been associated with the development of the insulin resistance syndrome and of type 2 **diabetes**, and with their associated cardiovascular diseases. This dietary shortfall has been exacerbated by the worldwide increase intake of refined foods. . .

SUMM [0433] Cr supplementation improves the diabetic control afforded by exercise. Supplements of **chromium** nicotinate or picolinate complexes lower blood sugar, LDL cholesterol and increase lean body mass. Cr supplementation can reduce metformin requirements. . .

SUMM . . . supplying the necessary cysteine intracellularly. GSH and glutathione peroxidase levels are notably reduced in progressive insulin resistance and type 2 **diabetes**. The deficiencies and the associated peroxide-mediated damage to cell membranes may appear early in the progressive insulin resistance and type 2 **diabetes**, before the development of secondary complications. Additionally, GSH counterbalances the effects of ICAM-1, one of the most important intercellular adhesion molecules involved with the atherogenesis associated with insulin resistance syndrome and type 2 **diabetes** . GSH similarly reduces thrombin activation, which results from hyperglycemia.

SUMM . . . and other elements of this invention, have the potential to delay the onset and delay the progression of "type 1.5 **diabetes** ". In the latter, ROS destroy pancreatic .beta.-cells. This .beta.-cells destruction results in the addition of insulin-dependent (type 1) **diabetes** mellitus clinical findings to those already existing from type 2 **diabetes**. Activation of NFkappaB by ROS-induced release of mitochondrial cytochrome C seems to be the key cellular signal in initiating a. . . of the prodrug NAC or .alpha.-lipoic acid)--a key intracellular regulator of NF-kappaB--affords protection against the insidious onset of "type 1.5 **diabetes**". In this context, supplementation with 500 mg/kg of NAC as a GSH precursor, has been shown to inhibit alloxan-induced NFkappaB. . . By inference, NFkappaB activation by ROS (via the mitochondria) may initiate a sequence of events eventually leading to type 1 **diabetes**, by way of "type 1.5 **diabetes**": In one study, inhibition of NF-kappaB activation by NAC has been shown to attenuate the severity of type 1 **diabetes**.

SUMM . . . sulfate, which may contribute to its thrombogenic property, which also potentially exacerbates the diminished heparan sulfate synthesis commonly observed in **diabetes** (See above.). A circular problem is therefore initiated in **diabetes**: homocysteine reduces heparan sulfate in the glomerulus, which leads to renal malfunction, which in turn leads to hyperhomocysteinemia, which aggravates the hypertension and thromboangiogenesis of **diabetes** , etc.

SUMM [0444] Hyperhomocysteinemia is associated with macrovascular disease in a significant proportion of patients with type 2 **diabetes**. Furthermore, this hyperhomocysteinemia is related to 5-year mortality rates independent of other major risk factors, and is a stronger (1.9-fold). . .

SUMM . . . that is essential for its structural integrity; the latter results in the vascular leakage associated with the devastating

microangiopathies of **diabetes**.

SUMM [0447] **Diabetes** significantly lowers folate in kidney, heart, brain, and muscle. The addition of metformin worsens this loss. For this reasons adjunct folate supplementation to combined treatment with sulfonylurea-metformin in progressive insulin resistance and type 2 **diabetes** is logical.

SUMM [0448] .alpha.-Lipoic acid is an important adjunct in sulfonylurea-metformin treatment for insulin resistance syndrome and type 2 **diabetes**. It increases insulin sensitivity, prevents depletion of GSH, limits protein glycation and attenuates NFkappaB transcription.

SUMM . . . acid and indirectly regenerates .alpha.-tocopherol. It increases intracellular GSH and limits protein glycation. It has the potential favorably to modify **diabetes** and reduce **diabetes**-induced complications, particularly diabetic neuropathy.

SUMM . . . and AA. .alpha.-lipoic acid seems to reduce AGE albumin-induced NF-kappaB mediated transcription and the expression of relevant endothelial genes in **diabetes**. Among others these include, tissue factors for VCAM-1 and for endothelin-1. Thus, in vitro supplementation of cellular antioxidative defense mechanisms. . .

SUMM . . . of events leading to .beta.-cell death. This, plus .alpha.-lipoate's enhancement of pancreatic GSH, affords protection against progression from type 2 **diabetes** to "type 1.5 **diabetes**".

SUMM . . . administered it increases the effectiveness, efficiency, and safety of sulfonylurea-metformin combinations in the prevention and treatment of insulin resistance and **diabetes** mellitus and expands the scope of sulfonylurea-metformin treatment to include macrovascular diabetic complications. Sulfonylurea-metformin pharmacokinetics do not appear to be. . .

SUMM [0457] The American **Diabetes** Association recommends that all patients with normal renal function who have hypomagnesemia and **diabetes** mellitus receive Mg.sup.2+ supplementation. This represents a majority of patients with progressive insulin resistance or type 2 **diabetes**. Mg.sup.2+ deficiencies are widespread in the progressive insulin resistance and type 2 **diabetes**. Patients receiving sulfonylurea exhibit little change in urinary excretion of Mg.sup.2+ yet they show a significant rise in serum Mg.sup.2+.. . .

SUMM . . . sulfonylurea and metformin on magnesium levels is unclear, their pharmacodynamic complementarity for patients with progressive insulin resistance or type 2 **diabetes** is fortunate, since both hyperinsulinemia and hyperglycemia can result in hypomagnesemia, which in turn increases insulin resistance--another vicious cycle.

SUMM [0459] Hypomagnesemia occurs in 25-38% of patients with type 2 **diabetes**. Current dietary amounts of Mg.sup.2+ are marginal. The average dietary intake of 450 to 485 mg per day of Mg.sup.2+. . . population dietary Mg.sup.2+ shortfall of 90 to 180 mg per day. Unfortunately for patients with insulin resistance and type 2 **diabetes**, circulating insulin (and perhaps proinsulin) induce an increase in the renal excretion of Mg.sup.2+. This might partly explain the Mg.sup.2+. . .

SUMM . . . the depletion of free Mg.sup.2+. Mg.sup.2+ supplementation should improve both insulin sensitivity and insulin secretion in patients with type 2 **diabetes**.

SUMM [0461] Decreased cellular Mg.sup.2+ concentrations represent a risk factor in the pathogenesis of both microvascular and macrovascular complications of **diabetes**. Low serum and dietary Mg.sup.2+ may be related to the etiologies of CVHD, hypertension, and atherosclerosis as well as progressive insulin resistance and type 2 **diabetes**. One of the most serious complications of **diabetes**, cardiac irregularity, including ventricular ectopic beats, is associated with

decreased intracellular Mg.sup.2+.

SUMM . . . importantly illustrates the synergistic and synergetic relationships that can (and must) be addressed by approaching insulin resistance and type 2 **diabetes** as nonlinear complexities, as is done by this invention.

SUMM [0464] In addition to complementary effects of Mg.sup.2+ with .alpha.-tocopherol and GSH in **diabetes**, similar synergisms for Mg.sup.2+ have been defined with taurine, carnitine and **vanadium**, and with sulfonylurea-metformin.

SUMM [0466] The inadequate intracellular Mg.sup.2+ concentration often found in progressive insulin resistance and type 2 **diabetes** results in defective tyrosine-kinase activities at the insulin receptor level and exaggerated intracellular Ca.sup.2+concentration. Daily Mg.sup.2+ administration to type 2 **diabetes** patients restores intracellular Mg.sup.2+ concentration and can contribute to improved insulin-mediated glucose uptake.

SUMM . . . potent antioxidant action similar to SOD. Some studies have shown that melatonin protects against oxidative stress and the severity of **diabetes** induced by STZ. Two activities are becoming apparent: 1) the powerful antioxidant action of this indole and, 2) the importance. . .

SUMM [0471] TNF-.alpha. has an important role in the development of insulin resistance, and type 2 **diabetes** and its progressive vascular complications. It can be favorably modified by melatonin. Cytokine production, including TNF-.alpha., in human whole blood. . . could fail to reduce the cytokine surge adequately and be detrimental in patients with progressive insulin resistance or type 2 **diabetes**. This may foster well-known, diabetic microvascular and macrovascular complications.

SUMM [0472] Melatonin also reduces the visceral fat that is associated with progressive insulin resistance and type 2 **diabetes**. Thus its supplementation provides an important adjunct to enhance the weight loss potential of metformin.

SUMM [0473] Visceral fat and plasma insulin levels increase with aging, and are associated with progressive insulin resistance and type 2 **diabetes**. Since melatonin favorably modulates visceral fat and the nighttime cytokine surge, melatonin supplementation may potentially provide an important adjunct to. . .

SUMM . . . inducible isoform of nitric oxide synthase (iNOS), an important contributor to the pathophysiology of inflammation, including the macrovascular complications of **diabetes** and pancreatic .beta.-cell destruction. Melatonin reduces iNOS steady-state mRNA levels and iNOS protein. This inhibition of iNOS expression is associated. . . of the transcription factor nuclear factor kappa B (NFkappaB), which has been associated with pancreatic .beta.-cell apoptosis in type 1 **diabetes**.(See above.) Additionally, melatonin decreases the production of nitrite/nitrate (the breakdown products of NO) in macrophages stimulated with bacterial lipopolysaccharide, reducing inflammation. These effects may be important in inhibiting the progression from type 2 **diabetes** to "type 1.5 **diabetes**", wherein there is an added immunologically driven .beta.-cell destruction superimposed on type 2 **diabetes**.

SUMM . . . of evidence indicates that melatonin production declines after age 45 in parallel with a statistically increasing occurrence of type 2 **diabetes**. It is reasonable to believe that the age-related loss of availability of melatonin and a subsequent reduction in capacity to reduce lipid peroxidation and AGEs, could be detrimental in type 2 **diabetes**. Supplemental melatonin as an adjunct to the clinical use of combination sulfonylurea-metformin treatment in progressive insulin resistance and type 2 **diabetes** is physiologically appropriate, and possibly should be made not only at night, but also during the day.

SUMM . . . both useful for reducing hypertriglyceridemia, thus having complementary potential in treating the dyslipidemia of progressive insulin resistance and type 2 **diabetes**.

SUMM [0478] Nicotinamide has value in preventing .beta.-cells destruction in type 1 **diabetes**. That there are beneficial effects in type 2 **diabetes** is not yet established, but prevention of progression from type 2 **diabetes** to "type 1.5 **diabetes**" seems likely, thus complementing sulfonylurea. Interleukin-1 beta (IL-1 beta) is known to inhibit glucose-induced insulin release by pancreatic islets. When. . .

SUMM [0479] Type 1 **diabetes** is caused by an immune-mediated destruction of the insulin-producing .beta.-cells. .beta.-cells are destroyed by induction of oxygen-derived free radicals and. . . can be demonstrated in the circulation. These antibodies can be detected up to eight years prior to overt type 1 **diabetes** and are also seen in some progressing type 2 diabetics (thus the name "type 1.5 **diabetes**"). Nicotinamide, a vitamin B.sub.3 derivative, interferes with the immune-mediated .beta.-cell destruction by reducing the content of free radicals and NO,. . .

SUMM [0482] Unfavorable rheological properties of blood, and abnormal red cell deformability, in **diabetes** are factors in its frequent microvascular complications. The improvements in blood rheology and in red cell deformability by .beta.-tocopherol nicotinate,. . . membrane of red blood cells. Treatment with .alpha.-tocopherol nicotinate may have complementary effects in slowing the microangiopathy of type 2 **diabetes**.

SUMM . . . (Amadori.fwdarw.Maillard reactions) leads to heterogeneous, toxic and antigenic AGEs and to reactive precursors that are implicated in the pathogenesis of **diabetes**. Pyridoxamine and thiamine pyrophosphate potently inhibit AGE formation, suggesting that these two compounds may have clinical potential in preventing vascular complications in type 2 **diabetes** and in insulin resistance.

SUMM [0487] Se, and more efficiently Se plus Vitamin E, supplementation in **diabetes** may play a role in controlling oxidative status and unfavorable lipid metabolism in the liver, thereby maintaining favorable fatty acid. . .

SUMM . . . while the exact mechanism is not clear, taurine also inhibits lipid peroxidation and decreases blood triglycerides and LDL-cholesterol levels in **diabetes**.

SUMM [0491] A deficient dietary level of taurine is associated with a variety of pathologies, including type 2 **diabetes**. Since 1981 taurine has been added to infant formulas and parental nutrition solutions in countries around the world and was. . .

SUMM . . . sensitivity, reducing hypercholesterolemia, inhibiting peroxidation of cell membrane components and modulating pericyte and other cell volume instabilities of type 2 **diabetes**. Its ACE inhibitor-like action adds an important dimension in modulating the characteristic hypertension of progressive insulin resistance and type 2 **diabetes**. The cardiac failure seen in later stages of these diseases may benefit from the mild cardiac glycoside-like effect of taurine,. . .

SUMM . . . protecting the pancreatic .beta.-cells from lipid peroxidation, thereby reducing the resulting .beta.-cell dysfunctional apoptosis that can lead to "type 1.5 **diabetes**".

SUMM [0496] Intracellular taurine declines with advancing age and in type 2 **diabetes**. This compounded decrease during both senescence and type 2 **diabetes** exacerbates age-related declines in antioxidant defense systems, Ca.sup.2+ regulation and membrane integrity. The actions of sulfonylurea in K.sup.+ channel blockade,. . . repolarized and is again receptive to sulfonylurea stimulation. However, taurine, carnitine and Mg.sup.2+ are all characteristically deficient in type 2 **diabetes**. This emphasizes the importance

of the use of formulations described in this invention as adjuncts to sulfonylurea-metformin therapy.

SUMM . . . disorganization and cellular dysfunction or death, all of which are aggravated by taurine deficiency. A number of the complications of **diabetes** are associated with or attributed to osmotic disruption of the cytoarchitecture. These may be lessened if there is adequate intracellular taurine and are worsened if there is a deficiency of taurine, as there often is in **diabetes**.

SUMM . . . that occurs in response to high glucose levels. An increase in TGF-.beta. is implicated in the pathogenesis of glomerulosclerosis in **diabetes**.

SUMM [0505] Approximately 80% of all patients with **diabetes** die of cardiovascular disease. Treatment with sulfonylurea-metformin has been ineffective in altering this dismal prognosis. Progressive insulin resistance, the fundamental defect of type 2 **diabetes** leads to hyperinsulinemia, which is associated with hypertension, atherogenic dyslipidemia, left ventricular hypertrophy, impaired fibrinolysis, visceral obesity, and a sedentary. . . conditions are associated with atherosclerosis and adverse cardiovascular events, the therapeutic effect of sulfonylurea and/or metformin treatment in patients with **diabetes** focuses solely on normalizing glucose levels and may even increase hyperinsulinemia, increasing the risk of cardiovascular events. Combined sulfonylurea-metformin therapy. . .

SUMM . . . destructive mechanisms involved with vascular endothelial damage and is at the root of many long-term complications of insulin resistance and **diabetes**, particularly nephropathy and retinopathy.

SUMM . . . the principal cause of the loss of cell membrane integrity in many pathologic states of vascular and neuronal cells, including **diabetes**. Tocopherol preserves SOD, involved in free radical hydrogen peroxide defense.

SUMM [0514] Increased oxidative stress, hypofibrinolysis and insulin resistance are present in obese type 2 **diabetes** patients. High doses of vitamin E (600 mg/day) used alone, may further worsen insulin efficiency and increase fibrinolysis in these. . .

SUMM . . . they increase the effectiveness, efficiency, and safety of combinations of sulfonylurea-metformin in the prevention and treatment of insulin resistance and **diabetes** mellitus and addresses their shortcomings in diabetic macrovascular disease.

SUMM **Vanadium**

SUMM [0521] Most patients with type 2 **diabetes** mellitus require pharmacotherapy, initially as monotherapy, subsequently in combination. Exogenous insulin is ultimately required in a substantial proportion, reflecting the. . .

SUMM [0522] **Vanadium** increases both hepatic and peripheral insulin sensitivity, thus expanding the activity of combinations of sulfonylurea-metformin. It also activates glycogenesis and. . .

SUMM [0523] **Vanadium** has therapeutic potential in both type 1 and type 2 **diabetes** in doses ranging from 0.083 mmol/d to 0.42 mmol/d. Although **vanadium** has significant biological potential, it has a poor (narrow) therapeutic index. Organic forms of **vanadium**, as opposed to the inorganic sulfate salt, may be safer, more absorbable, and may be able to deliver a therapeutic effect up to 50% greater than the inorganic forms. **Vanadium** has been administered to pregnant women diagnosed with pregnancy-induced **diabetes** without adverse effects upon either the mother or fetus.

SUMM [0524] **Vanadium** is present in a variety of foods that we commonly eat. The daily dietary intake in humans varies from 10 micrograms to 2 mg of elemental **vanadium**, depending on the sources available in various regions. The 100 mg/day often used in treating type 2 **diabetes** is clearly greater than

physiological, probably accounting for what is described as a narrow therapeutic index. Utilizing **vanadium** as one element in multicomponent formulations, as defined in this invention, will permit the dosage to be minimized and safety. . .

SUMM [0526] Vanadate (V.sup.5+), an oxidized form of **vanadium**, or vanadyl (V.sup.4+) promote both hepatic and peripheral insulin action by three mechanisms: 1) direct insulin-mimesis; 2) enhancement of insulin sensitivity and 3) prolongation of the insulin biological response. The insulin-mimetic action of these forms of **vanadium** persists after withdrawal of treatment. **Vanadium** treatment of non-diabetic animals lowers plasma insulin levels by reducing insulin demand, and these animals remain normoglycemic. Chronic treatment with **vanadium** has also been shown to result in sustained antidiabetic effects in STZ-diabetic animals long after treatment has ceased. Thus, 13 weeks after withdrawal from **vanadium** administration, treated animals have normalized glucose levels and normal weight gain, and improved basal insulin levels. In addition, near-normal glucose tolerance is found despite an insignificant insulin response. Since **vanadium** accumulates in several tissue sites when pharmacological doses are administered (e.g., bone, kidney), it is possible that stored **vanadium** may be important in maintaining near-normal glucose tolerance, at least in the short-term following withdrawal from treatment.

SUMM . . . 3 weeks of vanadyl sulfate (100 mg/day), both hepatic and peripheral insulin sensitivity appear to improve in insulin-resistant type 2 **diabetes** patients. These effects are sustained for up to 2 weeks after discontinuation of vanadyl sulfate.

SUMM [0529] **Vanadium** has several mechanisms of action in progressive insulin resistance and type 2 **diabetes**:

SUMM [0544] Tolerance does not appear to develop with long term oral administration of **vanadium**, but the safety of chronic **vanadium** treatment beyond five months is not yet established. This may have an impact on the therapeutic use of **vanadium**. To reduce this possibility of chronic use toxicity, the invention describes a pulsing of **vanadium** administration and/or once a day bedtime use to take advantage of the prolonged **vanadium** insulin-mimetic effect following withdrawal of treatment.

SUMM [0546] The relationship between **diabetes**, insulin and Zn.sup.2+ is complex. Functioning as an insulin cofactor, Zn.sup.2+ prevents hyperglycemia by increasing insulin activity at its receptor. . . tend to have low plasma Zn.sup.2+ concentrations and decreased total body Zn.sup.2+. Hyperglycemia, rather than any primary lesion related to **diabetes**, is responsible for increased urinary loss and a decrease in total body Zn.sup.2+, which in turn is in part responsible. . .

SUMM . . . control subjects, a significantly lower Cu, Zn-superoxide dismutase activity is found in both lymphocytes and polymorphonuclear cells of type 1 **diabetes** and type 2 **diabetes** patients. A Zn.sup.2+ deficiency can, therefore, reduce immunoefficiency or aggravate an existing immune deficiency, and contribute to the slow wound. . .

SUMM . . . patients with hypertension or congestive heart failure, but also for the prevention of the progression of renal dysfunction induced by **diabetes** mellitus.

SUMM . . . 24 to 3000 80 to 1200

L-Carnitine	90	to 2500	300	to 1000
Choline	15	to 250	50	to 100
Chromium	0.01	to 0.63	0.03	to 0.25
Folate	0.03	to 2.0	0.10	to 0.80
Lipoate	30	to 1500	100	to 600

. . . 15 to 1600 50 to 800

Tocotrienol	15	to 2000	50	to 800

Ubiquinone	4.5	to 225	15	to 90
Vanadium	7.5	to 375	25	to 150
Vitamin B12	0.001	to .010	0.002	to .004
Zinc	1.5	to 80	5	to. . .

DETD . . . and safety of combined sulfonylurea-metformin pharmaceuticals and combined sulfonylurea-like/metformin pharmaceutical agents, in the prevention and treatment of insulin resistance and **diabetes** mellitus, alone or in combination, as a nutrient for humans. The carefully chosen active ingredients of the invention act in. . . complementary biochemical partnership with sulfonylurea-metformin to avoid the development of, or ameliorate, progressive insulin resistance, to retard its progression to **diabetes** mellitus and to ensure an improvement in glucose tolerance, hypertension and obesity associated with type 2 **diabetes**, or a reduction in the morbidity rate; and that diabetic microvascular complications (nephropathy, retinopathy, neuropathy, etc.) as well as diabetic. . .

DETD [0612] Formulations designed for different aspects of progressive insulin resistance and type 2 **diabetes** processes are illustrated in the specifications and defined in the section on claims. Formulations will be used in appropriate sequencing,. . .

DETD . . . Illmer T et al. Advanced glycation end product-induced activation of NF-kappaB is suppressed by alpha-lipoic acid in cultured endothelial cells. **Diabetes** 1997; 46(9):1481-90.

DETD [0617] (4) DeFronzo R A. Pharmacologic therapy for type 2 **diabetes** mellitus. Ann Intern Med 1999; 131(4):281-303.

DETD . . . al. Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid/thioctic acid: participation of elements of the insulin signaling pathway. **Diabetes** 1996; 45(12): 1798-804.

DETD . . . Krohn K, Albers S, Meinertz T. Tetrahydrobiopterin improves endothelium-dependent vasodilation by increasing nitric oxide activity in patients with Type II **diabetes** mellitus. Diabetologia 2000; 43(11):1435-1438.

DETD . . . J H, Sharrett A R, Nabulsi A A et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, **diabetes**, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. J Clin Epidemiol 1995; 48(7):927-40.

CLM What is claimed is:

. . . for supporting mitochondrial metabolism as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) L-carnitine, (b) ascorbic acid, (c) choline,. . .

. . . membrane integrity for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) D,.alpha.-lipoic acid, (b) N, acetyl-cysteine, (c). . .

. . . specifically for nocturnal use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) melatonin, (b) L-carnitine, (c) Ubiquinone, (d). . .

. . . to insulin for use as a method for the prevention, management and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, said unit dosage form comprising as active ingredients: (a) **vanadium**, (b) L-arginine, (c) **chromium**, and (d) zinc.

12. A unit dosage form in accordance with claim 11 in which: (a) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (b) said L-arginine is in an amount ranging from about 75 mg to

about 3100 mg, (c) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, and (d) said zinc is in an. . . . layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
vanadium	40-60%	balance
L-arginine	40-60%	balance
chromium	40%-60%	balance
zinc	40%-60%	balance

23. A unit dosage form in accordance with claim 10 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

26. A unit dosage form in accordance with claim 10 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

. . . a patient who is undergoing biguanide therapy for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said biguanide therapy,. . .

. . . preservation of plasma and mitochondrial membrane integrity for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said biguanide therapy,. . .

. . . preservation of plasma and mitochondrial membrane integrity for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said biguanide therapy,. . .

. . . biguanide therapy as an alternative to insulin for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said biguanide therapy, said method comprising administering to said patient a unit dosage form comprising as active ingredients: (a) **vanadium**, (b) L-arginine, (c) **chromium**, and (d) zinc.

38. A method in accordance with claim 37 in which: (a) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, and (d) said zinc is in an. . . . layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
vanadium	40-60%	balance
L-arginine	40-60%	balance

chromium	40%-60%	balance
zinc	40%-60%	balance

49. A method in accordance with claim 36 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

52. A method in accordance with claim 36 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

. . . a patient who is undergoing sulfonylurea therapy for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said sulfonylurea therapy,. . .

. . . preservation of plasma and mitochondrial membrane integrity for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said sulfonylurea therapy,. . .

. . . preservation of plasma and mitochondrial membrane integrity for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said sulfonylurea therapy,. . .

. . . sulfonylurea therapy as an alternative to insulin for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said sulfonylurea therapy, said method comprising administering to said patient a unit dosage form comprising as active ingredients: (a) **vanadium**, (b) L-arginine, (c) **chromium**, and (d) zinc.

64. A method in accordance with claim 63 in which: (a) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, and (d) said zinc is in an. . .

. . . layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
vanadium	40-60%	balance
L-arginine	40-60%	balance
chromium	40%-60%	balance
zinc	40%-60%	balance

75. A method in accordance with claim 62 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

78. A method in accordance with claim 36 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

. . . biguanide and combined biguanide and sulfonylurea therapy for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said combined biguanide. . .

. . . preservation of plasma and mitochondrial membrane integrity for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said combined biguanide. . .

. . . preservation of plasma and mitochondrial membrane integrity for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said combined biguanide. . .

. . . sulfonylurea therapy as an alternative to insulin for the prevention, management, and clinical amelioration of insulin resistance and type 2 **diabetes** and conditions giving rise thereto, to reduce undesirable physiological side effects, and enhance the therapeutic effectiveness, of said combined biguanide and sulfonylurea therapy, said method comprising administering to said patient a unit dosage form comprising as active ingredients: (a) **vanadium**, (b) L-arginine, (c) **chromium**, and (d) zinc.

90. A method in accordance with claim 89 in which: (a) said **vanadium** is in an amount ranging from about 7.5 mg to about 375 mg, (b) said L-arginine is in an amount ranging from about 75 mg to about 3100 mg, (c) said **chromium** is in an amount ranging from about 0.01 mg to about 0.63 mg, and (d) said zinc is in an. . .

. . . layer and said sustained-release layer in the following approximate proportions expressed as relative weight percents:

	Immediate-Release Layer	Sustained-Release Layer
vanadium	40-60%	balance
L-arginine	40-60%	balance
chromium	40%-60%	balance
zinc	40%-60%	balance

101. A method in accordance with claim 88 in which said **vanadium** is in the form of a member selected from the group consisting of vanadate, peroxovanadate, vanadyl sulfate salts, and bis(maltolato)oxovanadium(IV).

. . .

104. A method in accordance with claim 88 in which said **chromium** is in the form of a member selected from the group consisting of **chromium** dinicotinate, and **chromium** tripicolinate.

L2 ANSWER 3 OF 4 USPATFULL
AN 2002:259463 USPATFULL
TI Methods and compositions for the treatment of alopecia and other disorders of the pilosebaceous apparatus
IN Krajcik, Rozlyn A., Poughquag, NY, UNITED STATES
Orentreich, Norman, New York, NY, UNITED STATES
PA Orentreich Foundation for the Advancement of Science, Inc., New York, NY, UNITED STATES (U.S. corporation)
PI US 2002143039 A1 20021003
AI US 2002-73607 A1 20020211 (10)
RLI Continuation of Ser. No. WO 2001-US5653, filed on 23 Feb 2001, UNKNOWN

PRAI US 2000-184398P 20000223 (60)
DT Utility
FS APPLICATION
LREP AKIN, GUMP, STRAUSS, HAUER & FELD, L.L.P., ONE COMMERCE SQUARE, 2005 MARKET STREET, SUITE 2200, PHILADELPHIA, PA, 19103
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 772
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Insulin sensitivity increasing substances (ISIS), including but not limited to D-chiro-inositol, **thiazolidinedione** and derivatives, and biguanides, are useful in the treatment of hair loss and other disorders of the pilosebaceous apparatus (hirsutism,. . .
SUMM [0006] In one embodiment, the ISIS is a member of a class of compounds termed **thiazolidinediones**, including derivatives thereof.
SUMM . . . which can lead to high triglyceride and free fatty acid levels. Also, diets deficient in such supplements as magnesium, copper, **chromium**, **vanadium**, and others can lead to insulin resistance. Additionally, metabolic acidosis can reduce the effectiveness of insulin.
SUMM [0019] In one embodiment, the ISIS is a member of the class of compounds termed **thiazolidinediones**, including derivatives thereof. Examples of such compounds include, troglitazone, ciglitazone, pioglitazone, rosiglitazone, and englitazone. The **thiazolidinediones** are known compounds and are described for example in B. B. Lohray et al., "Novel Euglycemic and Hypolipidemic Agents," J.. . . bibliography thereof; S. V. Edelmann, M.D., "Troglitazone: A New and Unique Oral Anti-Diabetic Agent for the Treatment of Type II **Diabetes** and the Insulin Resistance Syndrome," Clinical **Diabetes**, pp. 60-65 (March/April 1997); U.S. Pat. No. 5,594,015 of Kurtz et al.; and J. R. White et al., "Insulin Sensitizers,". . .
SUMM . . . so important as compliance (i.e., faithful use). The steroidal compounds are usually longer acting than metformin or D-chiro-inositol or even **thiazolidinediones**. Therefore, once daily dosing of most ARB/STI, in contrast to more frequent (twice or thrice daily) ISIS dosing, may be. . .
DETD . . . (Glucophage.RTM., Bristol-Myers Squibb Co., Princeton, N.J.) is a biguanide ISIS used clinically for the treatment of type II (non-insulin dependent) **diabetes** (refer to packaging insert for metformin). The antihyperglycemic effect of metformin has been ascribed to increased peripheral glucose disposal, suppression of glucose production by the liver and a decreased rate of intestinal glucose absorption (Hermann, L. S., **Diabetes** Metab. 5:233-245 (1979)). The plasma insulin level is not increased. In animal studies with the obese (ob/ob -Thieller background) mouse,. . .
CLM What is claimed is:
9. The method of claim 1, wherein said ISIS is a **thiazolidinedione**.

10. The method of claim 9, wherein said **thiazolidinedione** is selected from the group consisting of troglitazone, ciglitazone, pioglitazone, rosiglitazone, and englitazone.

21. The composition of claim 20, wherein said ISIS is a **thiazolidinedione**.

L2 ANSWER 4 OF 4 USPATFULL
AN 2002:88529 USPATFULL
TI Metforimin-containing compositions for the treatment of **diabetes**

IN Fine, Stuart A., Northbrook, IL, United States
Kinsella, Kevin J., La Jolla, CA, United States
PA Akesis Pharmaceuticals, Inc., La Jolla, CA, United States (U.S. corporation)
PI US 6376549 B1 20020423
AI US 1998-156102 19980917 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Criares, Theodore J.
LREP Foley, Hoag & Eliot LLP
CLMN Number of Claims: 40
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1429
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Metforimin-containing compositions for the treatment of **diabetes**
AB Compositions and methods using same for the treatment of **diabetes** its sequelae and pre-diabetic conditions are provided. Invention compositions include the anti-diabetic agent metformin, and bioavailable sources of one or more of **chromium**, **vanadium** and magnesium. Also provided are pharmaceutical agents containing invention compositions and methods for administering such agents.
SUMM . . . conditions. Particularly, this invention relates to metformin-containing pharmaceutical compositions and to methods of using the same for the treatment of **diabetes** and a number of symptoms which precede and/or accompany **diabetes**.
SUMM **Diabetes** mellitus is a mammalian condition in which the amount of glucose in the blood plasma is abnormally high. Elevated glucose. . . condition can be life-threatening and high glucose levels in the blood plasma (hyperglycemia) can lead to a number of chronic **diabetes** syndromes, for example, atherosclerosis, microangiopathy, kidney disorders or failure, cardiac disease, diabetic retinopathy and other ocular disorders, including blindness.
SUMM **Diabetes** mellitus is known to affect at least 10 million Americans, and millions more may unknowingly have the disease. There are two forms of the disease. In the form of this disease known as Type II, non-insulin dependent **diabetes** (NIDDM) or adult-onset (as opposed to juvenile **diabetes** or Type I), the pancreas often continues to secrete normal amounts of insulin. However, this insulin is ineffective in preventing the symptoms of **diabetes** which include cardiovascular risk factors such as hyperglycemia, impaired carbohydrate (particularly glucose) metabolism, glycosuria, decreased insulin sensitivity, centralized obesity hypertriglyceridemia,. . . various cardiovascular effects attending these risk factors. Many of these cardiovascular risk factors are known to precede the onset of **diabetes** by as much as a decade. These symptoms, if left untreated, often lead to severe complications, including premature atherosclerosis, retinopathy,. . .
SUMM Current drugs used for managing Type II **diabetes** and its precursor syndromes, such as insulin resistance, fall within five classes of compounds: the biguanides, **thiazolidinediones**, the sulfonylureas, benzoic acid derivatives and .alpha.-glucosidase inhibitors. The biguanides, e.g., metformin, are believed to prevent excessive hepatic gluconeogenesis. The **thiazolidinediones** are believed to act by increasing the rate of peripheral glucose disposal. The sulfonylureas, e.g., tolbutamide and glyburide, the benzoic. . .
SUMM Currently, there is no composition for the treatment of **diabetes**, its precursor syndromes and related sequelae that combines metformin with bioavailable elemental nutritional supplements such as **vanadium**, magnesium and **chromium** as well as other non-elemental nutritional palliatives which are effective in managing

diabetes, its precursors, and sequelae.

SUMM . . . containing one or more nutritional supplements in an amount sufficient to produce a desirable effect, such as bioavailable sources of **vanadium**, **chromium**, magnesium, vitamin E, lipoic acid, folate and the like. Additionally, compositions of the present invention may contain aspirin. The present invention improves upon current regimens for treating **diabetes** with metformin, by exploiting the insulin-like effects of **vanadium** and **chromium** and also by providing a source of magnesium, which is so often deficient in people with **diabetes**. Also provided are methods for the treatment of **diabetes** and conditions attending or commonly preceding **diabetes**, comprising administration of an effective amount of the aforementioned compositions.

SUMM In accordance with the present invention, there are provided compositions comprising metformin, one or more of a bioavailable source of **chromium**, **vanadium** or magnesium and pharmaceutically acceptable salts thereof; and a physiologically acceptable carrier.

SUMM . . . in addition to the aforementioned components, an effective amount of one or more additional anti-diabetic agents such as insulin, a **thiazolidinedione**, a sulfonylurea, a benzoic acid derivative, an .alpha.-glucosidase inhibitor, exendin-4, or the like. As will be apprecitated by those skilled. . .

SUMM . . . in the practice of the present invention. Generally, a fixed dosage regimen is individualized for the management of hyperglycemia in **diabetes** mellitus with metformin HCl or any other pharmacologic agent. Individualization of dosage is made on the basis of both effectiveness. . . be less than 100 mg per day when administered with higher amounts of bioavailable forms of two or more of **chromium**, **vanadium** or magnesium.

SUMM **Thiazolidinediones** contemplated for use in the practice of the present invention include troglitazone, and the like. Effective amounts of troglitazone, when. . .

SUMM As readily recognized by those of skill in the art, a variety of sulfonylureas are useful for the treatment of **diabetes**. Exemplary sulfonylureas contemplated for use in the practice of the present invention (with typical daily dosages indicated in parentheses) include. . .

SUMM . . . readily recognized by those of skill in the art, a variety of alpha-glucosidase inhibitors are useful for the treatment of **diabetes**. Exemplary alpha-glucosidase inhibitors contemplated for use in the practice of the present invention include acarbose, miglitol, and the like. Effective. . .

SUMM . . . recognized by those of skill in the art, a variety of benzoic acid derivatives are useful for the treatment of **diabetes**. Exemplary benzoic acid derivatives contemplated for use in the practice of the present invention include repaglinide (effective daily dosage in. . .

SUMM It has been discovered that administration of bioavailable forms of nutritional supplements such as **chromium**, **vanadium**, and magnesium are able to alleviate one or more symptomologies associated with **diabetes** or which indicate a predisposition to **diabetes**. As will be understood by those skilled in the art, "bioavailable," as used herein, conotes that a particular element or. . . incorporated or be otherwise physiologically available by the individual to whom it is administered. Any bioavailable sources of the elements **chromium**, **vanadium** and magnesium are contemplated for use in the practice of the present invention.

SUMM Bioavailable sources of **vanadium**, such as vanadyl sulfate, and of **chromium**, such as **chromium** picolinate, have properties that closely mimic, as well as enhance, many of the physiological effects of insulin because it has. . . and lowers blood

lipid and cholesterol levels. By their ability to potentiate the effects of insulin, both vanadyl sulfate and **chromium** have been found to enhance the entry of glucose (for energy) and amino acids (for protein synthesis) into muscle cells. . .

SUMM The combination of vanadate and **chromium** enhances the ability of insulin to utilize glucose. Vanadate ions, like insulin, stimulate glucose transport, activate glycogen synthase, increase glycogen. . .

SUMM **Chromium**, like **vanadium**, possesses properties that both mimic and enhance the effects of insulin. **Chromium** enhances the effects of insulin by indirectly assisting amino acid uptake by muscle, stimulating protein synthesis, and retarding the rate of protein breakdown. **Chromium** also lowers serum triglycerides. Yet, many clinical studies utilizing **chromium** as a nutritional supplement have shown only modest improvements in glucose tolerance due to poor absorption of nutritional (trivalent) **chromium**. In this respect, trivalent **chromium** has a strongly positive charge that impedes its movement across cell membranes. Due to the presence of competing ions such as copper, iron, manganese and zinc in the human body, adequate absorption of **chromium** occurs best when the metal is associated with a chelating agent such as picolinic acid. Because of its unique structure, picolinic acid binds tightly to transition metals such as zinc, manganese, and **chromium**, thereby neutralizing their positive charges and expediting their movement across cell membranes. Thus, compounds such as **chromium** picolinate and/or **chromium** polynicotinate are particularly useful as bioavailable **chromium** sources.

SUMM Trivalent **chromium** is an essential micronutrient required mainly for maintenance of normal glucose tolerance. Bioavailable sources of **chromium** include one or more of **chromium** picolinate, **chromium** polynicotinate, as well as other bioavailable forms of **chromium** known in the art or developed in the future, particularly forms of **chromium** that are chelated to an organic anion thus forming a membrane permeable complex that is more permeable than **chromium** alone. In one embodiment of the present invention, in the range of about 10 .mu.g up to about 400 .mu.g of elemental **chromium** equivalent is present per daily dose. As used herein "elemental **chromium** equivalent" refers to the amount of elemental **chromium** present in the particular complex (e.g. **chromium** picolinate) chosen for a given formulation of invention compositions. In one embodiment of the present invention, in the range of about 30 .mu.g up to about 5000 .mu.g **chromium** picolinate and/or **chromium** polynicotinate is present per daily dose. In another embodiment of the present invention, in the range of about 200 .mu.g up to about 4000 .mu.g **chromium** picolinate and/or **chromium** polynicotinate is present per daily dose. In a preferred embodiment, about 3264 .mu.g of **chromium** picolinate and/or **chromium** polynicotinate is present per daily dose.

SUMM **Vanadium** is a group V transition element that exists in several oxidation states (+2, +3, +4, and +5). Both vanadyl (+4). . . may be used to alleviate diabetic and pre-diabetic symptomology, with the vanadyl form being better tolerated physiologically. Bioavailable sources of **vanadium** include vanadyl sulfate, as well as other bioavailable forms of **vanadium** known in the art or developed in the future, particularly forms of **vanadium** that are chelated to an organic anion thus forming a membrane permeable complex that is more permeable than **vanadium** alone. In one embodiment of the present invention, vanadyl sulfate is present in the range of about 50 mg up. . .

SUMM Vitamin E improves the action of insulin, glucose metabolism and lipid levels. People with **diabetes** have been shown to have reduced

plasma vitamin E concentrations. As many as 60% of the newly diagnosed diabetic patients. . . has been shown to result in strong increase in total glucose disposal and in non-oxidative glucose metabolism in people with **diabetes**.

SUMM In accordance with another aspect of the present invention, there are provided methods for the treatment of a subject having **diabetes** mellitus, said method comprising administering to said subject an effective amount of a composition comprising metformin and one or more of a bioavailable source of **chromium**, **vanadium**, or magnesium, or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the. . .

SUMM In accordance with another embodiment of the present invention there are provided methods for the treatment of a subject having **diabetes** mellitus, said method comprising administering to said subject an effective amount of a composition comprising metformin and one or more of a bioavailable source of **chromium**, **vanadium**, or magnesium, or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier, said method further comprising monitoring said subject's. . .

SUMM As will be appreciated by those of skill in the art, **diabetes** presents a complicated array of conditions and symptoms including abnormal glucose metabolism, insulin resistance, hyperinsulinemia, hyperglycemia, hypertriglyceridemia, elevated LDL, lowered. . .

SUMM In addition, there are a number of precursor conditions which portend the development of **diabetes** and which can be treated by administration of invention compositions as described herein. Therefor, in accordance with another aspect of. . .

SUMM . . . a a glucose metabolism enhancing amount of a composition comprising metformin and one or more of a bioavailable source of **chromium**, **vanadium**, or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . subject a glucose level stabilizing amount of a composition comprising metformin and one or more of a bioavailable source of **chromium**, **vanadium**, or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . said subject a hyperglycemia reducing amount of a composition comprising metformin and one or more of a bioavailable source of **chromium**, **vanadium**, or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . subject blood sugar level stabilizing amount of a composition comprising metformin and one or more of a bioavailable source of **chromium**, **vanadium**, or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . said subject an insulin sensitizing amount of a composition comprising metformin and one or more of a bioavailable source of **chromium**, **vanadium**, or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . said subject an LDL lowering amount of a composition comprising metformin and one or more of a bioavailable source of **chromium** , **vanadium**, or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . said subject an HDL raising amount of a composition comprising metformin and one or more of a bioavailable source of **chromium** , **vanadium**, or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations,

sources and amounts of the active. . .

SUMM . . . subject a serum triglyceride reducing amount of a composition comprising metformin and one or more of a bioavailable source of **chromium, vanadium,** or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . said subject blood pressure lowering amount of a composition comprising metformin and one or more of a bioavailable source of **chromium, vanadium,** or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. All combinations, sources and amounts of the active. . .

SUMM . . . another aspect of the present invention there are provided methods for reducing the doseage of anti-diabetic medication such as a **thiazolidinedione,** a sulfonylurea, an .alpha.-glucosidase inhibitor or a benzoic acid derivative, said method comprising administering to said subject an effective amount of a composition comprising metformin and one or more of a bioavailable source of **chromium, vanadium,** or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. Optionally, said method further comprises monitoring the subject's. . .

SUMM . . . another aspect of the present invention, there is provided an improvement over methods for the treatment of a subject having **diabetes** by administering to said subject an effective amount of insulin, the improvement comprising administering to said subject an insulin need reducing amount of a composition comprising metformin and one or more of a bioavailable source of **chromium, vanadium,** or magnesium, a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. Optionally, said method further comprises monitoring the subject's. . .

DETD Effect of Administration of Invention Composition to Patient with **Diabetes**

DETD To test the efficacy of invention compositions, a supplement (detailed below) was administered daily to a female with type II **diabetes** who was experiencing poor blood sugar control while taking metformin 500 mg b.i.d.

DETD

Chromium 333 .mu.g (in the form of 1 mg Cr-picolinate)
Magnesium 46 mg (in the form of 384 mg MgCl)
Vanadyl-sulfate hydrate 100. . .

DETD Effect of Administration of Invention Composition to Patient with **Diabetes**

DETD . . . efficacy of invention compositions, a supplement (detailed below) was administered daily to a 27 year old female with type II **diabetes** who was experiencing poor blood sugar control while taking metformin 1000 mg b.i.d.

DETD

Chromium 333 .mu.g (in the form of 1 mg Cr-picolinate)
Magnesium 46 mg (in the form of 384 mg MgCl)
Vanadyl-sulfate hydrate 100. . .

CLM What is claimed is:

1. A composition for the treatment of **diabetes,** said composition comprising metformin; one or more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically treat **diabetes.**

2. A composition according to claim 1, wherein said bioavailable source

of **chromium** is one or more of **chromium** picolinate or **chromium** polynicotinate.

3. A composition according to claim 1, wherein said bioavailable source of **vanadium** is vanadyl sulfate.

7. A composition according to claim 2, wherein the amount of **chromium** polynicotinate is from about 30 .mu.g up to about 5000 .mu.g, per dose.

8. A composition according to claim 2, wherein the amount of **chromium** picolinate is from about 30 .mu.g up to about 1000 .mu.g, per dose.

19. A composition according to claim 18, wherein said anti-diabetic agent is insulin, a **thiazolidinedione**, a sulfonylurea, an .alpha.-glucosidase inhibitor or a benzoic acid derivative.

21. A composition according to claim 19, wherein said **thiazolidinedione** is troglitazone.

25. A method for the treatment of **diabetes** mellitus in a subject having **diabetes** mellitus, said method comprising administering to said subject an effective amount of a composition comprising metformin; one or more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically treat **diabetes** mellitus.

. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically treat elevated HbA1c levels in a subject having elevated HbA1c levels.

. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically treat daily blood glucose fluctuations in a subject susceptible to daily blood. . .

. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically improve the ability of a subject to metabolize glucose.

. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically reduce blood sugar levels in a subject susceptible to abnormal fluctuations in. . .

. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of

chromium and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically treat hyperglycemia in a subject having hyperglycemia.

. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically treat insulin resistance syndrome in a subject having insulin resistance syndrome.

. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components synergistically reduce the dosage of anti-diabetic medication needed for treatment of a diabetic. . .
36. A method according to claim 35, wherein said anti-diabetic medication is one or more of insulin, a **thiazolidinedione**, a sulfonylurea, an .alpha.-glucosidase inhibitor or a benzoic acid derivative.

38. In a method for the treatment of **diabetes** in a subject having **diabetes** by administering to said subject an effective amount of insulin, the improvement comprising administering to said subject an insulin need. . . more of a bioavailable source of magnesium and pharmaceutically acceptable salts thereof; one or more of a bioavailable source of **chromium** and pharmaceutically acceptable salts thereof; and one or more of a bioavailable source of **vanadium** and pharmaceutically acceptable salts thereof; which components of said composition synergistically reduce the effective amount of insulin needed.

```
=> S L1 AND VANADIUM?
         39970 VANADIUM?
L3          66 L1 AND VANADIUM?

=> S L3 AND PD<2002
       2999978 PD<2002
                 (PD<20020000)
L4           7 L3 AND PD<2002

=> D L4 1-7 KWIC, BIB

L4   ANSWER 1 OF 7  USPATFULL
PI     US 2001051645      A1   20011213                                <--
AB     The invention provides thiazolidinedione, oxadiazolidinedione,
       and triazolone compounds of Formula (I) which compounds are thyroid
       receptor ligands.   ##STR1##
AB     . . . such compounds and methods of treating obesity, overweight
       condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin
       disorders, thyroid disease, hypothyroidism, thyroid cancer,
       diabetes, atherosclerosis, hypertension, coronary heart disease,
       congestive heart failure, hypercholesterolemia, depression, and
       osteoporosis using such compounds.
SUMM   [0002] The present invention relates to certain
       thiazolidinedione, oxadiazolidinedione, and triazolone compounds
```

which are thyroid receptor ligands.

SUMM [0003] The invention further relates to pharmaceutical compositions and kits comprising such **thiazolidinedione**, oxadiazolidinedione, and triazolone compounds and to methods of using such compounds in the treatment of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesterolemia, depression, and osteoporosis.

SUMM [0011] Obesity is a major health risk that leads to increased mortality and incidence of Type 2 **diabetes** mellitus, hypertension, and dyslipidemia. In the United States, more than 50% of the adult population is overweight, and almost 1/4. . .

SUMM . . . treat obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias (including atrial and ventricular arrhythmias), skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesterolemia, depression, and osteoporosis.

SUMM . . . characterized by an impaired glucose metabolism that manifests itself in, inter alia, elevated glucose levels in patients suffering therefrom. Generally, **diabetes** is classified into two distinct subgroups:

SUMM [0014] (1) Type 1 **diabetes**, or insulin-dependent **diabetes** mellitus (IDDM), which arises when patients lack .beta.-cells producing insulin in their pancreatic glands, and

SUMM [0015] (2) Type 2 **diabetes**, or non-insulin dependent **diabetes** mellitus (NIDDM), which occurs in patients with, inter alia, impaired .beta.-cell function.

SUMM . . . the causative agent or disorder is unknown. While such so-called "essential" hypertension is often associated with disorders such as obesity, **diabetes** and hypertriglyceridemia, the relationship between these disorders has not yet been elucidated. Additionally, many patients display the symptoms of high. . .

SUMM [0024] The instant invention provides certain **thiazolidinedione**, oxadiazolidinedione, and triazolone compounds of structural Formula (I), the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the. . .

SUMM . . . of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias (including atrial and ventricular arrhythmias), skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesterolemia, depression, and osteoporosis.

SUMM . . . of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias (including atrial and ventricular arrhythmias), skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesterolemia, depression, and osteoporosis.

SUMM . . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, in a mammal which comprises administering to said. . . provides such methods wherein the condition is obesity. More preferably, the present invention provides such methods wherein the condition is **diabetes**.

SUMM . . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer,

diabetes, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, which methods comprise administering to a patient having. . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, a therapeutically effective amount of:

SUMM . . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis. More preferably, the present invention provides such methods. . .

SUMM . . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, which kits comprise:

SUMM . . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis; and

SUMM . . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis.

SUMM [0099] Also provided are methods of treating **diabetes**, which methods comprise administering to patients having, or at risk of having, **diabetes**, a therapeutically effective amount of a compound of Formula (I), a stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt. . .

SUMM [0100] In a preferred embodiment of the methods of treating **diabetes**, the **diabetes** is Type I **diabetes**.

SUMM [0101] In another preferred embodiment of the methods of treating **diabetes**, the **diabetes** is Type II **diabetes**.

SUMM [0148] In one aspect, the present invention concerns the treatment of **diabetes**, including impaired glucose tolerance, insulin resistance, insulin dependent **diabetes** mellitus (Type I), and non-insulin dependent **diabetes** mellitus (NIDDM or Type II). Also included in the treatment of **diabetes** are diabetic complications related thereto, including neuropathy, nephropathy, retinopathy, cataracts, and the like.

SUMM [0149] The preferred type of **diabetes** to be treated by the compounds of Formula (I), the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers, or prodrugs, is non-insulin dependent **diabetes** mellitus, i.e. NIDDM.

SUMM [0150] **Diabetes** can be treated by administering to a patient having **diabetes** (Type I or Type II), insulin resistance, impaired glucose tolerance, or any of the diabetic complications such as neuropathy, nephropathy,. . .

SUMM [0151] Representative agents that can be used to treat **diabetes** in combination with the compounds of Formula (I), the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the. .

. 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: L-386,398; lipid-lowering agents: benfluorex; antiobesity agents: fenfluramine; vanadate and **vanadium** complexes (e.g. Naglivan.RTM.) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG. . .

SUMM . . . class of compounds that have become well known for their utility in preventing and treating conditions arising from complications of **diabetes** including, for example, diabetic neuropathy and nephropathy. Such compounds are well known to one of ordinary skill in the art. . .

SUMM . . . and prodrugs. Aldose reductase inhibition is readily determined by those skilled in the art according to standard assays (J. Malone, **Diabetes**, 29, 861-864 (1980) "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are described herein,. . .

SUMM . . . an excess, or deficiency, of glucocorticoids in the body. As such, they may be used to treat the following: obesity, **diabetes**, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, glaucoma, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), neurodegeneration (for example,. . .

SUMM [0322] Preparation of **thiazolidinedione** derivatives 1-6 and 1-7 is illustrated in Scheme 1. The key intermediate diaryl ether 1-3 can be synthesized by coupling. . . aldehyde 1-4 by manganese dioxide. The aldehyde reaction product so produced may then be reacted via a Knoevengel condensation with **thiazolidinedione** in the presence of a catalytic amount of piperidinium acetate to afford benzylidene **thiazolidinedione** 1-5. Demethylation of the condensation product 1-5 with boron tribromide gives phenol 1-6. Hydrogenation of 1-5 gives the saturated benzyl **thiazolidinedione** which reacts with boron tribromide to furnish phenol 1-7. ##STR10##

SUMM . . . with DIBAL furnishes the corresponding alcohol which is oxidized to benzaldehyde 2-3 with manganese dioxide. Condensation of aldehyde 2-3 with **thiazolidinedione** produces an intermediate benzylidene **thiazolidinedione** which is hydrogenated to furnish benzyl **thiazolidinedione** 2-4. A subsequent chlorosulfonylation reaction yields a 3'-sulfonyl chloride which is then reacted with a primary or secondary amine to. . .

SUMM . . . bromide 3-6. Oxidation of benzyl bromide 3-6 with N-methylmorpholine N-oxide in acetonitrile yields benzaldehyde 3-7 which is converted into benzyl **thiazolidinedione** 3-9 by Knoevenagel condensation followed by hydrogenation. ##STR12##

DETD [0339] To a suspension of the title compound from Step B (60 mg, 0.18 mmol) and **thiazolidinedione** (21 mg, 0.18 mmol) in dry toluene (2 ml) was added a catalytic amount of piperidinium acetate which was generated. . .

DETD . . . To a solution of the title compound of Step B (284 mg, 0.96 mmol) in toluene (16 ml) was added 2,4-**thiazolidinedione** (140 mg, 1.2 mmol), a catalytic amount of piperidinium acetate which was generated from piperidine (five drops) and acetic acid. . .

DETD [0399] To a solution of the title compound of Step H (40 mg, 0.10 mmol) and **thiazolidinedione** (13 mg, 0.11 mmol) in toluene (2 ml) was added acetic acid (1.5 .mu.l, 0.025 mmol), piperidine (2.5 .mu.l, 0.025. . .

CLM What is claimed is:

. . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, in a mammal

which method comprises administering to. . .
9. A method according to claim 7 wherein said condition is **diabetes**.

12. A method of treating a condition selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, which method comprises administering to a patient having,. . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, a therapeutically effective amount of: 1) a compound. . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis.

. . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis, wherein said kit comprises: a) a first pharmaceutical. . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis; and c) a container.

. . . selected from the group consisting of obesity, overweight condition, hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, thyroid disease, hypothyroidism, thyroid cancer, **diabetes**, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, hypercholesteremia, depression and osteoporosis.

AN 2001:229692 USPATFULL|
TI Thyroid receptor ligands|
IN Chiang, Yuan-Ching P., East Lyme, CT, United States
PI US 2001051645 A1 20011213 <--
AI US 2001-836765 A1 20010417 (9)
PRAI US 2000-199044P 20000421 (60)
DT Utility|
FS APPLICATION|
LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340|
CLMN Number of Claims: 25|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 3216|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 2 OF 7 USPATFULL
TI Method and composition for the treatment of **diabetes**
PI US 6153632 20001128 <--
AB This invention is directed to a novel method and composition for the treatment of **diabetes** mellitus (Type I, Impaired Glucose Tolerance ["IGT"]and Type II). More specifically, this invention

pertains to a novel method of treating **diabetes** mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of **diabetes** mellitus.

SUMM This invention is directed to a novel method and composition for the treatment of **diabetes** mellitus (Type I, Impaired Glucose Tolerance ["IGT"]and Type II). More specifically, this invention pertains to a novel method of and compositions for orally treating **diabetes** mellitus by administering to a person afflicted with **diabetes** mellitus one or more sensitizer chemicals, which increase the cells ability to utilize glucose, along with orally ingested medications for the treatment of **diabetes** mellitus.

SUMM It is estimated that 1.5 to 2% of the entire population of the world suffers from **diabetes** mellitus of some type. **Diabetes** mellitus is a chemical disorder of the human body primarily involving an inability of the body to properly utilize sugar. . .

SUMM In general terms, **diabetes** mellitus is classified into three types, namely, Type I, IGT and Type II. In Type I **diabetes**, the beta cells in the pancreas, probably through an auto-immune reaction, cease producing insulin into the bloodstream of the person.. . .

SUMM In IGT and Type II **diabetes**, the pancreas continues to produce insulin but, some or all of the insulin may fail to bind to the body's. . .

SUMM The existence of Type I, IGT or Type II **diabetes** in a person is usually determined by an oral glucose tolerance test (OGTT). OGTT is a test in which the. . .

SUMM 9. Vanadyl Sulfate (**Vanadium** Oxysulfate).

SUMM . . . is being conducted to develop an insulin which can be orally ingested for the treatment of Type I or II **diabetes**. Such an orally ingestible insulin would be welcomed by Type I and Type II diabetics because it would no longer. . .

SUMM IGT and Type II **Diabetes** can be treated with one or more classes of drugs generally known as hypoglycaemics to reduce blood glucose levels.

SUMM U.S. Pat. No. 4,362,719 --Therapeutic Method and Compositions for the Treatment of Juvenile **Diabetes** Mellitus

SUMM U.S. Pat. No. 4,826,684 --Composition for, and Method of, Treatment of **Diabetes**

SUMM U.S. Pat. No. 5,187,154 --Diagnosis and Treatment of Humans with **Diabetes** or at Risk to Develop **Diabetes**

SUMM U.S. Pat. No. 5,380,526 --Antidiabetic Agent and Method of Treating **Diabetes**

SUMM U.S. Pat. No. 5,468,755 --Therapeutic Process for the Treatment of the Pathologies of Type II **Diabetes**

SUMM U.S. Pat. No. 5,478,852 --Use of **Thiazolidinedione** Derivatives and Related Antihyperglycemic Agents in the Treatment of Impaired Glucose Tolerance in Order to Prevent or Delay the Onset of Noninsulin-Dependent **Diabetes** Mellitus

SUMM U.S. Pat. No. 5,589,183 --Method and Apparatus for Treatment of Neurogenic **Diabetes** Mellitus, and Other Conditions

SUMM U.S. Pat. No. 5,595,763 --Tungsten (VI) Compositions for the Oral Treatment of **Diabetes** Mellitus

SUMM The invention is directed to a method and composition for the treatment of **diabetes** mellitus including Type I, IGT and Type II **diabetes** mellitus. More specifically, this invention pertains to a novel method of treating **diabetes** mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of **diabetes** mellitus. A therapeutic amount of

insulin sensitizer can comprise one microgram to 10 grams of one or more insulin sensitizers. . .

SUMM The invention is directed to a method for the treatment of **diabetes** mellitus comprising administering to a person afflicted with **diabetes** mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of a drug selected from the group consisting. . .

SUMM The invention is also directed to a composition for the treatment of **diabetes** mellitus comprising: (a) a therapeutic amount of an insulin sensitizer; and (b) a therapeutic amount of a drug selected from. . .

SUMM The addition of an insulin sensitizer to drugs used for the treatment of **diabetes** mellitus reduces the required dosage of these drugs due to the increased uptake of glucose facilitated by the insulin sensitizer.

SUMM My discovery has application to other **diabetes** treatments, methods and drugs. When a sulfonylurea is used to stimulate insulin production and control **diabetes** mellitus, including an insulin sensitizer with the sulfonylurea, less of the sulfonylurea is required to achieve the same therapeutic effect. . .

SUMM When a biguanide is used to control **diabetes** mellitus, the amount of the biguanide required can be reduced and yet the same blood glucose levels in the body. . .

SUMM My discovery can also be applied to alpha-glucosidase inhibitors. When an alpha-glucosidase inhibitor is used to control **diabetes** mellitus, less of the alpha-glucosidase inhibitor is required to achieve the same blood glucose levels in the body when an. . .

DETD . . . in combination with an orally ingestible insulin should enable the orally ingestible insulin to work effectively in the treatment of **diabetes** mellitus. This is because the levels of insulin that must ultimately reach the bloodstream are greatly reduced, and such low. . .

CLM What is claimed is:

1. A composition for the treatment of **diabetes** mellitus comprising: (a) a therapeutic amount of an insulin sensitizer; and (b) a therapeutic amount of an anti-diabetic agent.

5. A composition for the treatment of **diabetes** mellitus in a mammal comprising: (a) a therapeutically effective amount of an orally ingestible insulin which is formulated to withstand. . .

6. A composition for the treatment of **diabetes** mellitus comprising: (a) a therapeutically effective amount of an injected insulin; and, (b) a therapeutically effective amount of one or. . .

16. A method for the treatment of **diabetes** mellitus comprising administering to a person afflicted with **diabetes** mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of an anti-diabetic agent.

21. A method for the treatment of **diabetes** mellitus comprising administering to a person afflicted with **diabetes** mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of an orally ingestible anti-diabetic agent, wherein (1). . .

AN 2000:161029 USPATFULL|
TI Method and composition for the treatment of **diabetes**|
IN Rieveley, Robert B., 4102 Yuculta Crescent, Vancouver, British Columbia, Canada V6N 3R5
PI US 6153632 20001128 <--
AI US 1997-804903 19970224 (8)
DT Utility|
FS Granted|
EXNAM Primary Examiner: Weddington, Kevin E.|
LREP Oyen Wiggs Green & Mutala|

CLMN Number of Claims: 24|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 497|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 3 OF 7 USPATFULL
PI US 6080770 20000627 <--
SUMM . . . with a concomitant increase in the level of phosphotyrosine in cellular proteins leading to transformation (Karlund, Cell 41: 707-717 (1985)). **Vanadium**-based phosphatase inhibitors are relatively unspecific. Therefore, to assess the importance of specific structures on PTPase activity more selective inhibitors are. . .
SUMM PTPases: the insulin receptor signalling pathway/**diabetes**
SUMM . . . and plays a key role in the control of blood glucose. Defects related to its synthesis or signalling lead to **diabetes** mellitus. Binding of insulin to its receptor causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the. . . other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden et al., J. Biol. Chem. 267: 16660-16668 (1992); Myers and White, **Diabetes** 42: 643-650 (1993); Lee and Pilch, Am. J. Physiol. 266: C319-C334 (1994); White et al., J. Biol. Chem. 263: 2969-2980. . .
SUMM . . . and as immunostimulants. One recent study illustrates the potential of PTPase inhibitors as immunmodulators by demonstrating the capacity of the **vanadium**-based PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Schieven et al., J. Biol. Chem.. . .
SUMM . . . to inhibit of PTPases involved in regulation of the insulin receptor tyrosine kinase signalling pathway in patients with type I **diabetes**, type II **diabetes**, impaired glucose tolerance, insulin resistance, and obesity. Further preferred embodiments include use of the compounds of the invention for treatment. . .
DETD Example 21 ##STR32## 5-(3-(Biphenyl-4-ylmetoxy)benzylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above benzaldehyde (5.00 g, 17 mmol), 2,4-**thiazolidinedione** (3.03 g, 26 mmol) and piperidine (0.35 ml, 3.5 mmol) in ethanol (75 ml) was stirred at reflux temperature for. . .
DETD Example 22 ##STR33## 5-((9-(4-Phenylbenzyl)-9H-carbazol-3-yl)-methylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above carboxaldehyde (2.00 g, 5.5 mmol), 2,4-**thiazolidinedione** (0.97 g, 8.3 mmol) and piperidine (0.11 ml, 1.1 mmol) in ethanol (50 ml) was stirred at reflux temperature for. . .
AN 2000:80778 USPATFULL
TI Modulators of molecules with phosphotyrosine recognition units
IN Andersen, Henrik Sune, Kobenhavn O, Denmark
Moller, Niels Peter Hundahl, Kobenhavn O, Denmark
Madsen, Peter, Bagsvaerd, Denmark
PA Novo-Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6080770 20000627 <--
AI US 1999-253419 19990219 (9)
RLI Division of Ser. No. US 1997-842801, filed on 16 Apr 1997
PRAI DK 1996-464 19960419
US 1996-22116P 19960717 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Oswecki, Jane C.
LREP Zelson, Steve T., Rozek, Carol E.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 2055
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 4 OF 7 USPATFULL
PI US 6063800 20000516 <--
SUMM . . . with a concomitant increase in the level of phosphotyrosine in cellular proteins leading to transformation (Klarlund, Cell 41: 707-717 (1985)). **Vanadium**-based phosphatase inhibitors are relatively unspecific. Therefore, to assess the importance of specific structures on PTPase activity more selective inhibitors are. . .
SUMM PTPases: the Insulin Receptor Signalling Pathway/**Diabetes**
SUMM . . . and plays a key role in the control of blood glucose. Defects related to its synthesis or signalling lead to **diabetes** mellitus. Binding of insulin to its receptor causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the. . . other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden et al., J. Biol. Chem. 267: 16660-16668 (1992); Myers and White, **Diabetes** 42: 643-650 (1993); Lee and Pilch, Am. J. Physiol. 266: C319-C334 (1994); White et al., J. Biol. Chem. 263: 2969-2980. . .
SUMM . . . and as immunostimulants. One recent study illustrates the potential of PTPase inhibitors as immunmodulators by demonstrating the capacity of the **vanadium**-based PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Schieven et al., J. Biol. Chem.. . .
SUMM . . . to inhibit of PTPases involved in regulation of the insulin receptor tyrosine kinase signalling pathway in patients with type I **diabetes**, type II **diabetes**, impaired glucose tolerance, insulin resistance, and obesity. Further preferred embodiments include use of the compounds of the invention for treatment. . .
DETD Example 21 ##STR29## 5-(3-(Biphenyl-4-ylmetoxy)benzylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above benzaldehyde (5.00 g, 17 mmol), 2,4-**thiazolidinedione** (3.03 g, 26 mmol) and piperidine (0.35 ml, 3.5 mmol) in ethanol (75 ml) was stirred at reflux temperature for. . .
DETD Example 22 ##STR30## 5-((9-(4-Phenylbenzyl)-9H-carbazol-3-yl)-methylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above carboxaldehyde (2.00 g, 5.5 mmol), 2,4-**thiazolidinedione** (0.97 g, 8.3 mmol) and piperidine (0.11 ml, 1.1 mmol) in ethanol (50 ml) was stirred at reflux temperature for. . .
CLM What is claimed is:
8. A compound according to claim 1 selected from the following; 5-(Difluoro-(4-(2-(methyl-pyridin-2-yl-amino)ethoxy)-phenyl)-methyl)-thiazolidine-2,4-dione; 5-((4-(2-(5-Ethyl-pyridin-2-yl)-ethoxy)-phenyl)-difluoro-methyl)-thiazolidine-2,4-dione; 5-((2-benzyl-chroman-6-yl)-difluoro-methyl)-thiazolidine-2,4-dione; 5-(Difluoro-(4-(3-(5-methyl-2-phenyl-oxazol-4-yl)-propionyl)-phenyl)-methyl)-thiazolidine-2,4-dione; 5-(Difluoro-(4-(2-hydroxy-2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy)-phenyl)-methyl)-thiazolidine-2,4-dione; 5-(Difluoro-(4-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl-methoxy)-phenyl)-methyl)-thiazolidine-2,4-dione; 5-(3-(Biphenyl-4-ylmetoxy)benzylidene)-2,4-**thiazolidinedione**; 5-((9-(4-Phenylbenzyl)-9H-carbazol-3-yl)-methylidene)-2,4-thiazolidenedione or a pharmaceutically acceptable salt thereof.

AN 2000:61616 USPATFULL|
TI Modulators of molecules with phosphotyrosine recognition units|
IN Andersen, Henrik Sune, Kobenhavn O, Denmark
Moller, Niels Peter Hundahl, Kobenhavn O, Denmark

Madsen, Peter, Bagsvaerd, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6063800 20000516 <--
AI US 1999-253443 19990219 (9)
RLI Division of Ser. No. US 1997-842801, filed on 16 Apr 1997
PRAI DK 1996-464 19960419
US 1996-22116P 19960717 (60)
DT Utility|
FS Granted|
EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Oswecki, Jane C.|
LREP Zelson, Steve T., Rozek, Carol E.|
CLMN Number of Claims: 9|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 2073|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 5 OF 7 USPATFULL
PI US 5972978 19991026 <--
SUMM . . . with a concomitant increase in the level of phosphotyrosine in cellular proteins leading to transformation (Klarlund, Cell 41: 707-717 (1985)). **Vanadium**-based phosphatase inhibitors are relatively unspecific. Therefore, to assess the importance of specific structures on PTPase activity more selective inhibitors are. . .
SUMM PTPases: the Insulin Receptor Signalling Pathway/**Diabetes**
SUMM . . . and plays a key role in the control of blood glucose. Defects related to its synthesis or signalling lead to **diabetes** mellitus. Binding of insulin to its receptor causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the. . . other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden et al., J. Biol. Chem. 267: 16660-16668 (1992); Myers and White, **Diabetes** 42: 643-650 (1993); Lee and Pilch, Am. J. Physiol. 266: C319-C334 (1994); White et al., J. Biol. Chem. 263: 2969-2980. . .
SUMM . . . and as immunostimulants. One recent study illustrates the potential of PTPase inhibitors as immunmodulators by demonstrating the capacity of the **vanadium**-based PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Schieven et al., J. Biol. Chem.. . .
SUMM . . . to inhibit of PTPases involved in regulation of the insulin receptor tyrosine kinase signalling pathway in patents with type I **diabetes**, type II **diabetes**, impaired glucose tolerance, insulin resistance, an d obesity. Further preferred embodiments include use of the compounds of the invention for. . .
DETD Example 21 ##STR29## 5-(3-(Biphenyl-4-ylmetoxy)benzylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above benzaldehyde (5.00 g, 17 mmol), 2,4-**thiazolidinedione** (3.03 g, 26 mmol) and piperidine (0.35 ml, 3.5 mmol) in ethanol (75 ml) was stirred at reflux temperature for. . .
DETD Example 22 ##STR30## 5-((9-(4-Phenylbenzyl)-9H-carbazol-3-yl)-methylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above carboxaldehyde (2.00 g, 5.5 mmol), 2,4-**thiazolidinedione** (0.97 g, 8.3 mmol) and piperidine (0.11 ml, 1.1 mmol) in ethanol (50 ml) was stirred at reflux temperature for. . .
AN 1999:132860 USPATFULL
TI Modulators of molecules with phosphotyrosine recognition units
IN Andersen, Henrik Sune, Kobenhavn, Denmark
Moller, Niels Peter Hundahl, Kobenhavn, Denmark
Madsen, Peter, Bagsvaerd, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 5972978 19991026 <--

AI US 1999-252883 19990219 (9)
RLI Division of Ser. No. US 1997-842801, filed on 16 Apr 1997
PRAI DK 1996-464 19960419
US 1996-22116P 19960717 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Oswecki, Jane C.
LREP Zelson, Steve T., Rozek, Carol E.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2078
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 6 OF 7 USPATFULL
PI US 5958957 19990928 <--
SUMM . . . with a concomitant increase in the level of phosphotyrosine in cellular proteins leading to transformation (Klarlund, Cell 41: 707-717 (1985)). **Vanadium**-based phosphatase inhibitors are relatively unspecific. Therefore, to assess the importance of specific structures on PTPase activity more selective inhibitors are. . .
SUMM PTPases: the Insulin Receptor Signalling Pathway/**Diabetes**
SUMM . . . and plays a key role in the control of blood glucose. Defects related to its synthesis or signalling lead to **diabetes** mellitus. Binding of insulin to its receptor causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the. . . other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden et al, J. Biol. Chem. 267: 16660-16668 (1992); Myers and White, **Diabetes** 42: 643-650 (1993); Lee and Pilch, Am. J. Physiol. 266: C319-C334 (1994); White et al., J. Biol. Chem. 263: 2969-2980. . .
SUMM . . . and as immunostimulants. One recent study illustrates the potential of PTPase inhibitors as immunmodulators by demonstrating the capacity of the **vanadium**-based PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Schieven et al., J. Biol. Chem.. . .
SUMM . . . to inhibit of PTPases involved in regulation of the insulin receptor tyrosine kinase signalling pathway in patients with type I **diabetes**, type 11 **diabetes**, impaired glucose tolerance, insulin resistance, and obesity. Further preferred embodiments include use of the compounds of the invention for treatment. . .
DETD Example 21 ##STR24## 5-(3-(Biphenyl-4-ylmetoxy)benzylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above benzaldehyde (500 g, 17 mmol), 2,4-**thiazolidinedione** (3.03 g, 26 mmol) and piperidine (0.35 ml, 3.5 mmol) in ethanol (75 ml) was stirred at reflux temperature for. . .
DETD Example 22 ##STR25## 5-((9-(4-Phenylbenzyl)-9H-carbazol-3-yl)-methylidene)-2,4-**thiazolidinedione**
DETD A mixture of the above carboxaldehyde (2.00 g, 5.5 mmol), 2,4-**thiazolidinedione** (0.97 g, 8.3 mmol) and piperidine (0.11 ml, 1.1 mmol) in ethanol (50 ml) was stirred at reflux temperature for. . .
AN 1999:117528 USPATFULL
TI Modulators of molecules with phosphotyrosine recognition units
IN Andersen, Henrik Sune, Copenhagen, Denmark
Moller, Niels Peter Hundahl, Copenhagen, Denmark
Madsen, Peter, Bagsvaerd, Denmark
PA Novo Nordisk A/S, Bassvaerd, Denmark (non-U.S. corporation)
PI US 5958957 19990928 <--
AI US 1997-842801 19970416 (8)
PRAI DK 1996-46469 19960419

DT Utility
FS Granted
EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Oswecki, Jane C.
LREP Zelson, Steve T., Lambiris, Elias J., Rozek, Carol E.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2103
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 7 OF 7 USPATFULL
TI Use of bisphenolic compounds to treat type II **diabetes**
PI US 5827898 19981027 <--
AB This invention is directed to methods for treatment of non-insulin-dependent **diabetes** mellitus, for reducing blood glucose levels, or hyperglycemia. The methods entail administering to a mammal in need of such treatment. . .
SUMM This invention relates to a novel method of treating Type II **diabetes**, a method for lowering the blood glucose levels and a method for treatment of hypoglycemia and hypoglycemia associated abnormalities in. . .
SUMM . . . extracts of dried branches or dried leaf or dried root of Larrea tridentata are used in Baja California to treat **diabetes** (Dimayuga, et al., 1987, supra; Winkelman, 1989, "Ethnobotanical Treatments of **Diabetes** in Baja California Norte," Medicinal Anthropology, 11:255-268).
SUMM . . . Several elder local informants of Baja California Sur recalled that Larrea tridentata was employed to treat foot infections, kidney pain, **diabetes**, high blood pressure, and headache (Dimayuga, et al., 1987, supra). These informants claimed that their knowledge of medicinal plants was. . .
SUMM . . . and to be a metabolic stimulant (French patent FR 3866M). Others have reported that 2,2'-alkylidene bisdialkyl phenols lower serum cholesterol. **Vanadium** and niobium complexes of a large variety of catechol derivatives including NDGA were claimed to be hypocholesterolemic, hypolipidemic and to be useful for the treatment of **diabetes** (PCT Publication No. WO 93/14751). However, these phenolic substances were present only as carriers for the metal ions and were. . .
SUMM . . . NDGA, its stereoisomers, analogs and derivatives as illustrated below, are effective in lowering blood sugar and in the treatment of **diabetes**, especially Type II **diabetes**.
SUMM This invention is directed to methods for treatment of non-insulin-dependent **diabetes** mellitus, for reducing blood glucose levels, or for treatment of hypoglycemia. The methods comprise administering to a mammal in need. . .
SUMM The invention also encompasses combination therapies. For example, this invention provides methods for treating non-insulin-dependent **diabetes** mellitus, treating hypoglycemia, or reducing blood glucose level, which comprise administering to a mammal in need of such treatment a. . .
SUMM According to another example, this invention provides methods for treating non-insulin-dependent **diabetes** mellitus, treating hypoglycemia, or reducing blood glucose level, which comprise administering to a mammal in need of such treatment a. . .
DETD This invention is directed to methods for treatment of non-insulin-dependent **diabetes** mellitus, for reducing blood glucose levels, and for treatment of hypoglycemia. The methods comprise administering to a mammal in need. . .
DETD The invention also encompasses combination therapies. For example, this invention provides methods for treating non-insulin-dependent **diabetes** mellitus, for treating hypoglycemia, or for reducing

blood glucose levels, which comprise administering to a mammal in need of such. . .

DETD According to another example, this invention provides methods for treating non-insulin-dependent **diabetes** mellitus, treating hypoglycemia, or reducing blood glucose level, which comprise administering to a mammal in need of such treatment a. . .

DETD Suitable biguanides include metformin and buformin; suitable sulfonylureas include acetohexamide, chlorpropamide, tolazamide, tolbutamide, glyburide, glypizide and glyclazide; suitable **thiazolidinediones** include troglitazone; .alpha.-glycosidase inhibitors include acarbose and miglatol; suitable .beta..sub.3 -adrenoceptor agonists include CL-316, 243, etc.

DETD As described above, the bisphenolic compounds are advantageously used to treat **diabetes**. Additionally, the bisphenolic compounds can advantageously be used as hypoglycemic agents to reduce the blood glucose level in situations of. . .

DETD . . . for example NDGA, produce a significant and consistent hypoglycemic effect on obese diabetic mice, i.e., an art recognized model of **diabetes** mellitus. Further demonstrated are NDGA's beneficial effects on glucose tolerance and the ability to stimulate glucose transport in adipocytes.

DETD . . . obese diabetic db/db mice, a model recognized by those skilled in the art as being a representative model of non-insulin-dependent **diabetes** mellitus (NIDDM).

DETD . . . obese diabetic ob/ob mice, a model recognized by those skilled in the art as being a representative model of non-insulin-dependent **diabetes** mellitus (NIDDM).

AN 1998:131760 USPATFULL

TI Use of bisphenolic compounds to treat type II **diabetes**

IN Khandwala, Atul S., San Carlos, CA, United States
Luo, Jian, Brisbane, CA, United States

PA Shaman Pharmaceuticals, Inc., South San Francisco, CA, United States (U.S. corporation)

PI US 5827898 19981027 <--

AI US 1996-726591 19961007 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Jordan, Kimberly

LREP Pennie & Edmonds LLP

CLMN Number of Claims: 3

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 824

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> D HIS

(FILE 'HOME' ENTERED AT 13:22:57 ON 14 MAY 2003)

FILE 'USPATFULL' ENTERED AT 13:23:29 ON 14 MAY 2003

L1 722 S THIAZOLIDINEDIONE? AND DIABETES

L2 4 S L1 AND VANADIUM? AND CHROMIUM?

L3 66 S L1 AND VANADIUM?

L4 7 S L3 AND PD<2002

=> S L1 AND CHROMIUM?

106644 CHROMIUM?

L5 30 L1 AND CHROMIUM?

=> S L5 AND PD<2000

2605798 PD<2000

(PD<20000000)
L6 13 L5 AND PD<2000

=> D L13 1-13 KWIC, BIB
L13 NOT FOUND
The L-number entered has not been defined in this session, or it has been deleted. To see the L-numbers currently defined in this session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> D L6 1-13 KWIC, BIB

L6 ANSWER 1 OF 13 USPATFULL
PI US 5972970 19991026 <--
SUMM . . . blood sugar and lipid in blood, to a method of producing it and to an agent for the therapy of **diabetes**, which is useful in the field of pharmaceuticals.
SUMM As remedies of **diabetes**, various biguanide compounds and sulfonylurea compounds have so far been used. However, biguanide compounds are hardly used at present, since. . . action of lowering blood sugar, often cause severe hypoglycemia, requiring special attention in use. On the other hand, there are **thiazolidinedione** derivatives and oxazolidinedione derivatives known to have actions of lowering blood sugar and lipid in blood, which are free of. . .
SUMM 3. a method for treating a mammal suffering from **diabetes** or hyperlipidemia, which comprises administering to the mammal an effective amount of a compound of the formula (I) or a. . .
SUMM . . . or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a mammal suffering from **diabetes** or hyperlipidemia,
SUMM . . . a composition with, for example, a per se known pharmacologically acceptable carrier, excipient and filler as a therapeutic agent of **diabetes** in mammals including man. Compound (I) or pharmaceutically acceptable salt thereof of the present invention also exhibits improving activity of. . .
SUMM . . . oxidation reaction is carried out by a known conventional manner such as Jones' oxidation using sulfuric acid-pyridine, Collins oxidation using **chromium** oxide-pyridine complex, oxidation using pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), oxidation using activated dimethyl sulfoxide (DMSO), oxidation using oxoammonium salt,. . .
DETD . . . derivatives (I) of the present invention exhibit excellent hypoglycemic and hypolipidemic actions, and are pharmaceutically useful as therapeutic agents for **diabetes**, hyperlipemia and hypertension, for example.
CLM What is claimed:
15. A medicinal composition for the treatment of **diabetes** or hyperlipidemia which comprises an effective amount of a compound or pharmaceutically acceptable salt thereof as defined in claim 1,. . .
17. A method for treating a mammal suffering from **diabetes** or hyperlipidemia, which comprises administering to the mammal an effective amount of a compound, or a pharmaceutically acceptable salt thereof. . .
AN 1999:132852 USPATFULL|
TI Oxazolidinedione derivatives, their production and use|
IN Sohda, Takashi, Takatsuki, Japan
Ikeda, Hitoshi, Higashiosaka, Japan
Momose, Yu, Takarazuka, Japan
Imai, Sachiko, Kyoto, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 5972970 19991026 <--
AI US 1997-832916 19970404 (8)
RLI Division of Ser. No. US 1995-554107, filed on 6 Nov 1995, now patented,

Pat. No. US 5665748 which is a continuation of Ser. No. US 1994-201021, filed on 24 Feb 1994, now abandoned
PRAI JP 1993-38236 19930226
JP 1993-197304 19930809
DT Utility|
FS Granted|
EXNAM Primary Examiner: Fan, Jane|
LREP Wenderoth, Lind & Ponack, L.L.P.|
CLMN Number of Claims: 17|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 2181|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 13 USPATFULL
PI US 5932601 19990803 <--
SUMM . . . and lipid in blood, to a method of producing it and to an agent comprising it for the therapy of **diabetes**, which is used in the field of pharmaceuticals.
SUMM As remedies of **diabetes**, various biguanide compounds and sulfonylurea compounds have so far been used. However, biguanide compounds are hardly used at present, since. . . action of lowering blood sugar, often cause severe hypoglycemia, requiring special attention in use. On the other hand, there are **thiazolidinedione** derivatives and oxazolidinedione derivatives known to have actions of lowering blood sugar and lipid in blood, which are free of. . .
SUMM . . . in combination with, for example, a per se known pharmacologically acceptable carrier, excipient and filler as a therapeutic agent of **diabetes** and an antihypertensive agent in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).
SUMM . . . in accordance with a per se known oxidation method, for example, the chromic acid oxidation such as Jones' oxidation using **chromium** oxide-sulfuric acid-pyridine, Collins' oxidation using **chromium** oxide-pyridine complex, oxidation using pyridinium chlorochromate (PCC) and oxidation using pyridinium dichloride (PDC); oxidation using activated DMSO or oxidation using. . .
DETD . . . above, oxazolidinedione derivatives (I) of the present invention exhibit excellent hypoglycemic and hypolipidemic actions in model mice suffering from noninsulin-dependent **diabetes** mellitus, and are pharmaceutically useful as therapeutic agents for **diabetes**, hyperlipemia and hypertension, among others.
CLM What is claimed is:
5. A method for treating **diabetes** in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound or. . .
11. A pharmaceutical composition according to claim 8, which is a therapeutic agent of **diabetes**.

AN 1999:89177 USPATFULL|
TI Oxazolidinedione derivatives, their production and use|
IN Sohda, Takashi, Takatsuki, Japan
Odaka, Hiroyuki, Kobe, Japan
Momose, Yu, Takarazuka, Japan
Kawada, Mitsuru, Amagasaki, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 5932601 19990803 <--
AI US 1995-550289 19951030 (8)
PRAI JP 1994-269826 19941102
JP 1995-171768 19950707
JP 1995-220942 19950829
DT Utility|

FS Granted|
EXNAM Primary Examiner: Daus, Donald G.|
LREP Wenderoth, Lind & Ponack L.L.P.|
CLMN Number of Claims: 17|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 2896|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 3 OF 13 USPATFULL
PI US 5843970 19981201 <--
SUMM 5-(4-[2-(5-methyl-4-phenyl-2-oxazoyl)ethoxy]benzyl)-2,4-**thiazolidinedione**; and,
SUMM 5-[4-(4-phenyl-2-thiazolylmethoxy)benzyl]-2,4-**thiazolidinedione**.
SUMM 5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione**; and,
SUMM 5-(4-[2-(5-bromomethyl-2-phenyl-4-oxazolyl)ethoxy]benzyl)-2,4-**thiazolidinedione**.
SUMM 5-(4-[2-(5-ethyl-2-pyridyl)-2-hydroxyethoxy]benzyl)-2,4-**thiazolidinedione**; and,
SUMM 5-(4-[2-hydroxy-2-(6-methyl-2-pyridyl)ethoxy]benzyl)-2,4-**thiazolidinedione**.
SUMM The **thiazolidinedione** may be further selected from compounds wherein Y and Z are oxo and R.sub.1 is selected from compounds of the. . .
SUMM . . . and are generally described as 5'-Aryl Substituted thiazolidine derivatives. These compounds are known to be useful for the treatment of **diabetes**.
SUMM . . . of reaction 1) together with Raney nickel alloy in aqueous formic acid. The product of reaction 2) reacts with the **thiazolidinedione** ring in a suitable solvent-base system. Suitable solvents include short chain alcohols, dimethyl-formamide, dimethylsulfoxide, sulfolane, acetonitrile, dioxane, dimethoxyethane or acetic. . .
SUMM The **thiazolidinedione** ring reactant in step 3) is made according to the procedure detailed in part A above.
SUMM . . . on the cyclohexane ring may be converted to the corresponding hydroxyl compounds by reduction. Preferable oxidizing agents are of the **chromium** trioxide species (e.g. Jones' reagent, **chromium** trioxide-pyridine) and preferable reducing agents are sodium borohydride and aluminum isopropoxide-isopropanol.
SUMM In the first step of the above synthetic scheme, approximately equimolar amounts of the carbonyl reactant and the **thiazolidinedione** are heated in the presence of a mild base to provide the olefin product. While this step may be carried. . .
SUMM In a typical such reaction the aldehyde or ketone starting material and **thiazolidinedione** are combined in approximately equimolar amounts with a molar excess, preferably a 2-4 fold molar excess, of anydrous sodium acetate. . .
AN 1998:150972 USPATFULL
TI Thiazolidine derivatives for the treatment of hypertension
IN Pershadsingh, Harrihar A., 2812 Burger St., Bakersfield, CA, United States 93305
Kurtz, Theodore W., 1251 Lattie La., Mill Valley, CA, United States 94941
PI US 5843970 19981201 <--
AI US 1991-725327 19910708 (7)
RLI Continuation-in-part of Ser. No. US 1989-421102, filed on 13 Oct 1989, now patented, Pat. No. US 5053420

DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Townsend and Townsend and Crew LLP
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1032
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 13 USPATFULL
PI US 5824694 19981020 <--
AB . . . use for certain thiazolidine derivatives is disclosed. Specifically, treatment of hyperproliferative epithelial cell conditions, such as psoriasis, by administration of **thiazolidinediones** or 5'-aryl substituted thiazolidine derivatives is described. Appropriate chemical structures, synthetic reactions, formulations, routes of administration and dosages are included.
SUMM This invention relates to an additional medical use of **thiazolidinediones**, some of which are used in the treatment of **diabetes** and essential hypertension. These compounds are also useful for the treatment of psoriasis and other diseases including acne.
SUMM The invention provides methods for the treatment of psoriasis by effective dosages of thiazolidine derivatives known as **thiazolidinediones**. These compounds can also be used according to the invention to treat other disorders involving epidermal or epithelial cell proliferation.. . .
SUMM The **thiazolidinediones** have the advantage over conventional therapy of targeting the problem of psoriatic epidermal hyperplasia without disrupting the immune system, predisposing. . .
SUMM In human keratinocytes proliferating in culture, according to the invention, the **thiazolidinedione** ciglitazone caused a dose-dependent inhibition of keratinocyte cell growth. Based on the discovery that **thiazolidinediones** have a potent ability to attenuate proliferation of human keratinocytes, the invention includes the novel approach of using these agents. . .
DETD . . . psoriasis. The active ingredients of the compositions are well-known compounds which are generally described as 5'-aryl substituted thiazolidine derivatives or **thiazolidinediones**. These compounds are conventionally known for the treatment of **diabetes**. Particular examples are ciglitazone, pioglitazone (also known as AD-4833 and U-72107E), englitazone (also known as CP-68,722), and troglitazone (also know. . .
DETD . . . Pancreatic Islets of Ob/Ob Mice, Metabolism, 37: 276-280 (1988); and Chang, A. Y. et al., Ciglitazone, A New Hypoglycemic Agent, **Diabetes** 32: 830-838 (1983).
DETD **Thiazolidinediones** conform to the following structural formula I: ##STR1## where variable ring substituents are defined below. A is H or methyl;
DETD 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-**thiazolidinedione** (commonly called pioglitazone);
DETD 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzoyl-2,4-**thiazolidinedione**.
DETD 5-{4-[2-(5-methyl-4-phenyl-2-oxazoyl)ethoxy]benzyl}-2,4-**thiazolidinedione**; and,
DETD 5-[4-(4-phenyl-2-thiazolylmethoxy)benzyl]-2,4-**thiazolidinedione** .
DETD 5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione** ;
DETD 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione**; and,

DETD 5-{4-[2-(5-bromomethyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione**.

DETD 5-{4-[2-(5-ethyl-2-pyridyl)-2-hydroxyethoxy]benzyl}-2,4-**thiazolidinedione**; and,

DETD 5-{4-[2-hydroxy-2-(6-methyl-2-pyridyl)ethoxy]benzyl}-2,4-**thiazolidinedione**.

DETD The **thiazolidinedione** may be further selected from compounds wherein Y and Z are oxo and R.sub.1 is selected from compounds of the. . .

DETD The **thiazolidinedione** may be further selected from compounds wherein Y and Z are oxo and R.sub.1 is selected from compounds of the. . .

DETD . . . of reaction 1) together with Raney nickel alloy in aqueous formic acid. The product of reaction 2) reacts with the **thiazolidinedione** ring in a suitable solvent-base system. Suitable solvents include short chain alcohols, dimethyl-formamide, dimethylsulfoxide, sulfolane, acetonitrile, dioxane, dimethoxyethane or acetic. . .

DETD The **thiazolidinedione** ring reactant in step 3) is made according to the procedure detailed in part A above.

DETD . . . on the cyclohexane ring may be converted to the corresponding hydroxyl compounds by reduction. Preferable oxidizing agents are of the **chromium** trioxide species (e.g. Jones' reagent, **chromium** trioxide-pyridine) and preferable reducing agents are sodium borohydride and aluminum isopropoxide-isopropanol.

DETD In the first step of the above synthetic scheme, approximately equimolar amounts of the carbonyl reactant and the **thiazolidinedione** are heated in the presence of a mild base to provide the olefin product. While this step may be carried. . .

DETD In a typical reaction, the aldehyde or ketone starting material and **thiazolidinedione** are combined in approximately equimolar amounts with a molar excess, preferably a 2-4 fold molar excess, of anydrous sodium acetate. . .

DETD An efficient one-step route to the sulfonyl-2,4-**thiazolidinediones** employed a selective C-5 sulfonylation of dilithio-2,4-**thiazolidinedione** upon treatment with a sulfonyl chloride is presented (Scheme I). See Zask, et al., J. Med. Chem. 33: 1418-1423 (1990),. . . formula XII are taken and which is incorporated herein by reference. The dianion was readily prepared by the treatment of 2,4-**thiazolidinedione** with 2 equivalents of n-butyllithium. An alternative two-step sequence utilized a base-mediated coupling of a thiol with 5-bromo-2,4-**thiazolidinedione** to provide the 5-thio intermediate, which was oxidized to the sulfone with an excess of hydrogen peroxide in acetic acid. . .

DETD The requisite 5-bromo-2,4-**thiazolidinedione** was obtained by bromination of 2,4-**thiazolidinedione** with bromine in acetic acid. In an analogous reaction, coupling of 2-naphthol with the **thiazolidinedione** in the presence of base gave the corresponding ether. Selective oxidation of the sulfide to the corresponding sulfoxide was effected. . .

DETD Selective N-methylation of the 2,4-**thiazolidinedione** ring was accomplished by treatment of naphthalene sulfone analogue with equimolar amounts of sodium hydride and iodomethane. Dimethylation of the. . . upon treatment with excess potassium carbonate and iodomethane. The C-5 methyl analogue was synthesized by preparation of the dianion of 5-methyl-2,4-**thiazolidinedione** followed by treatment with 1-naphthalenesolfonyl chloride.

DETD . . . to the 4-alkoxyphenyl sulfone analogue bearing the lipophilic alkoxy group found in ciglitazone utilized a nucleophilic displacement of fluoride from 5-[(fluoro-phenyl)sulfonyl]-2,4-**thiazolidinedione** by the alkoxide of (1-

methylcyclohexyl)methanol (Scheme II). Treatment of the **thiazolidinedione** with (1-methylcyclohexyl)methanol in dimethyl-formamide in the presence of sodium hydride gave the desired analogue.

DETD Method A. 5-[(Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione**. To a stirred solution of 2,4-**thiazolidinedione** (5.5 g, 47 mmol) in tetrahydrofuran (THF) (275 mL) at -78.degree. C. under nitrogen was added n-butyllithium (62 mL, 99. . . sulfate) and then concentrated to give an oil, which was purified by chromatography (acid-washed silica gel, 10:1 chloroform/acetonitrile) to give 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione** (7.6 g, 42% yield): mp 189.degree.-190.degree. C. (acetonitrile/chloroform): .sup.1 H NMR (DMSO-d.sub.6, 200 MHz) .delta. 6.60 (s, 1 H, CH,. . .

DETD Method B. 5-[(1-Bromo-2-naphthalenyl)thio]-2,4-**thiazolidinedione**. A solution of 5-bromo-2,4-**thiazolidinedione** (2.54 g, 13 mmol) and 1-bromo-2-mercaptonaphthalene (2.91 g, 13 mmol) in THF (100 mL) under nitrogen at -78.degree. C. was. . . (magnesium sulfate) and concentrated to give a yellow oil (5.27 g). Chromatography of this material (acid-washed silica gel, chloroform) gave 5-[(1-Bromo-2-naphthalenyl)thio]-2,4-**thiazolidinedione** (3.68 g, 83% yield): mp 128.degree.-129.degree. C. (hexane/ethyl acetate); .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta. 6.42 (s, 1 H,. . .

DETD Method C. 5-(2-Naphthalenylsulfonyl)-2,4-**thiazolidinedione**. To a solution of 5-(2-thianaphthalenyl)-2,4-thiazolidinedion (2.5 g, 9.1 mmol) in acetic acid (100 mL) at 60.degree. C. was added 30%. . . gel, 70:30 methanol/water) to give 2 as a foam (1.7 g, 62% yield). Crystallization from hexane/chloroform/methanol gave white needles of 5-(2-Naphthalenylsulfonyl)-2,4-**thiazolidinedione** (1.31 g, 47% yield): mp 196.degree.-197.degree. C.; .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta. 6.75 (s, 1 H CH, exchanges. . .

DETD 5-Bromo-2,4-**thiazolidinedione**. To a solution of 2,4-**thiazolidinedione** (100 g, 0.885 mol) in acetic acid (250 mL) at 85.degree. C. was added bromine (42.7 mL, 0.885 mol) dropwise. . . was filtered through a short column of silica gel (8:1 chloroform/acetonitrile). The resulting oil was triturated with hexane to give 5-Bromo-2,4-**thiazolidinedione** as a white powder (95.0 g, 57% yield): mp 61.degree.-62.degree. C.; .sup.1 H NMR (acetone-d.sub.6, 200 MHz) .delta. 6.41 (s,. . .

DETD 5-(2-Naphthalenyloxy)-2,4-**thiazolidinedione**. By a procedure similar to that of method B, a solution of 2-naphthol (5.0 g, 35 mmol) and 5-bromo-2,4-**thiazolidinedione** (6.8 g, 35 mmol) in THF (200 mL) was treated with lithium bis(tri-methylsilyl)amide (76 mL, 76 mmol, 1.0M in THF) to give, after chromatography (acid-washed silica gel, chloroform/acetonitrile), 5-(2-Naphthalenyloxy)-2,4-**thiazolidinedione** (2.8 g, 31% yield): mp 221.degree.-222.degree. C. (acetone/ethyl acetate); .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta. 6.52 (s, 1 H,. . .

DETD 5-(2-Naphthalenylsulfinyl)-2,4-**thiazolidinedione**. To a solution of 5-(2-thianaphthalenyl)-2,4-**thiazolidinedione** (1.0 g, 3.6 mmol) in dichloromethane (100 mL) was added m-chloroperbenzoic acid (0.74 g, 85%, 3.6 mmol) portionwise over 30. . . solid was washed repeatedly with hot carbon tetrachloride to remove m-chlorobenzoic acid. Recrystallization of the remaining solid (1.1 g) gave 5-(2-Naphthalenylsulfinyl)-2,4-**thiazolidinedione** as a 3:1 mixture of diastereomers (0.55 g, 52% yield): mp 157.degree.-158.degree. C. (acetonitrile/carbon tetrachloride); .sup.1 H NMR (DMSO-d.sub.6, 400. . .

DETD 5-[[4-[(1-Methylcyclohexyl)methoxy]phenyl]sulfonyl]-2,4-**thiazolidinedione**. Sodium hydride (3.17 g, 66.1 mmol, 50% in oil) was added to a solution of (1-methylcyclohexl)methanol (8.47 g, 66.1 mmol) in dimethylformamide (30 mL). The mixture was heated to

55.degree. C. for 30 minutes. A solution of 5-[(4-fluorophenyl)sulfonyl]-2,4-**thiazolidinedione** (1.82 g, 6.61 mmol) in dimethylformamide (20 mL) was then added. After 3 hours at 55.degree. C., the reaction mixture. . . The resulting white foam (1.31 g) was rechromatographed (acid-washed silica gel, chloroform) and then recrystallized from hexane/ethyl acetate/ether to give 5-[[4-[(1-Methylcyclohexyl)methoxy]phenyl]sulfonyl]-2,4-**thiazolidinedione** as a white powder (0.97 g, 38% yield) mp 174.degree.-175.degree. C.; .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta. 1.00 (s,. . .

DETD 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3-methyl-2,4-**thiazolidinedione**. To a solution of 5-[(Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione** (2.0 g, 5.2 mmol) in THF/dimethylformamide (1:1 40 mL) at 25.degree. C. under nitrogen was added sodium hydride (0.25 g,. . . phase was dried (magnesium sulfate) and concentrated to give crude product. Chromatography (silica gel, chloroform) and recrystallization (2.times. chloroform/ether) gave 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3-methyl-2,4-**thiazolidinedione** (520 mg, 25% yield): mp 150.degree.-151.degree. C. .sup.1 H NMR (CDCl.sub.3, 400 MHz) .delta. 3.03 (s, 3 H, CH.sub.3), 5.59. . .

DETD 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3,5-dimethyl-2,4-**thiazolidinedione**. To a solution of 5-[(Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione** (1.1 g, 2.9 mmol) in acetone (50 mL) at 25.degree. C. was added anhydrous potassium carbonate (3.9 g, 29 mmol). . . the mixture was filtered and the filtrate concentrated. Purification by chromatography (acid-washed silica gel, carboetetrachloride/chloroform) followed by recrystallization (chloroform/hexane/exane) gave 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3,5-dimethyl-2,4-**thiazolidinedione** (0.69 g, 59% yield): mp 160.degree.-161.degree. C. .sup.1 H NMR (CDCl.sub.3, 400 MHz) .delta. 2.10 (s, 3 H, CH.sub.3), 2.69. . .

DETD 5-[(6-Hydroxyl-2-naphthalenyl)thio]-2,4-**thiazolidinedione**. Potassium hydroxide (2.47 g, 44.0 mmol) was added to a suspension of 5-[(6-ethoxycarbonyloxy-2-naphthalenyl)thio]-2,4-**thiazolidinedione** (8.0 g, 22 mmol) in methanol (50 mL) at 25.degree. C. After 30 minutes, the resulting solution was acidified to. . . pH=1 with and then extracted with ethyl acetate (3.times.). The combined extracts were dried (magnesium sulfate) and concentrated to give 5-[(6-Hydroxyl-2-naphthalenyl)thio]-2,4-**thiazolidinedione** as a powder (6.4 g, 99% yield): mp 182.degree.-183.degree. C. (chloroform/ethyl acetate); .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta. 6.07. . .

DETD A preferred way to practice the invention is to apply the **thiazolidinedione** compound, in a cream or oil based carrier, directly to the psoriatic lesions. Typically, the concentration of therapeutic compopund in. . . cream or oil is 1-2%. Alternatively, an aerosol can be used topically. These compounds can also be orally administered. The **thiazolidinedione** compound trogitazone (Sankyo's CS-045 and Parke-Davis' CI-991), is an example of a **thiazolidinedione** that can be used in this fashion.

CLM What is claimed is:

12. A method of claim 2 wherein the **thiazolidinedione** is selected from compounds where R.sub.1 is of the formula XI ##STR65## wherein the broken line is a bond or. . .

AN 1998:128282 USPATFULL|

TI Thiazolidine derivatives for the treatment of psoriasis|

IN Kurtz, Theodore W., Mill Valley, CA, United States
Pershadsingh, Harrihar A., Bakersfield, CA, United States

PA Bethesda Pharmaceuticals, Inc., Mill Valley, CA, United States (U.S. corporation)

PI US 5824694 19981020 <--

AI US 1996-639942 19960418 (8)

RLI Continuation of Ser. No. US 1995-460384, filed on 2 Jun 1995, now abandoned And a continuation of Ser. No. US 1994-263446, filed on 22 Jun 1994, now patented, Pat. No. US 5594015
DT Utility|
FS Granted|
EXNAM Primary Examiner: Killos, Paul J.|
LREP Townsend and Townsend and Crew LLP|
CLMN Number of Claims: 21|
ECL Exemplary Claim: 1|
DRWN 15 Drawing Figure(s); 8 Drawing Page(s)|
LN.CNT 1806|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 5 OF 13 USPATFULL
PI US 5665748 19970909 <--
SUMM . . . blood sugar and lipid in blood, to a method of producing it and to an agent for the therapy of **diabetes**, which is useful in the field of pharmaceuticals.
SUMM As remedies of **diabetes**, various biguanide compounds and sulfonylurea compounds have so far been used. However, biguanide compounds are hardly used at present, since. . . action of lowering blood sugar, often cause severe hypoglycemia, requiring special attention in use. On the other hand, there are **thiazolidinedione** derivatives and oxazolidinedione derivatives known to have actions of lowering blood sugar and lipid in blood, which are free of. . .
SUMM 3. a method for treating a mammal suffering from **diabetes** or hyperlipidemia, which comprises administering to the mammal an effective amount of a compound of the formula (I) or a. . .
SUMM . . . or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a mammal suffering from **diabetes** or hyperlipidemia,
SUMM . . . a composition with, for example, a per se known pharmacologically acceptable carrier, excipient and filler as a therapeutic agent of **diabetes** in mammals including man. Compound (I) or pharmaceutically acceptable salt thereof of the present invention also exhibits improving activity of. . .
SUMM . . . oxidation reaction is carried out by a known conventional manner such as Jones' oxidation using sulfuric acid-pyridine, Collins oxidation using **chromium** oxide-pyridine complex, oxidation using pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), oxidation using activated dimethyl sulfoxide (DMSO), oxidation using oxoammonium salt,. . .
SUMM . . . derivatives (I) of the present invention exhibit excellent hypoglycemic and hypolipidemic actions, and are pharmaceutically useful as therapeutic agents for **diabetes**, hyperlipemia and hypertension, for example.
CLM What is claimed is:
11. A pharmaceutical composition for the treatment of **diabetes** or hyperlipidemia which comprises an effective amount of a compound or pharmaceutically acceptable salt thereof as defined in claim 1. . .
13. A method for the treatment of a mammal suffering from **diabetes** or hyperlipidemia which comprises administering to such mammal an effective amount of a compound or pharmaceutically acceptable salt as defined. . .
AN 97:81296 USPATFULL|
TI Oxazolidinedione derivatives and their use|
IN Sohda, Takashi, Takatsuki, Japan
Ikeda, Hitoshi, Higashiosaka, Japan
Momose, Yu, Takarazuka, Japan
Imai, Sachiko, Kyoto, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 5665748 19970909 <--

AI US 1995-554107 19951106 (8)
RLI Continuation of Ser. No. US 1994-201021, filed on 24 Feb 1994, now abandoned
PRAI JP 1993-38236 19930226
JP 1993-197304 19930809
DT Utility|
FS Granted|
EXNAM Primary Examiner: Fan, Jane|
LREP Wenderoth, Lind & Ponack|
CLMN Number of Claims: 13|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 2181|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 6 OF 13 USPATFULL
PI US 5594015 19970114 <--
AB . . . use for certain thiazolidine derivatives is disclosed. Specifically, treatment of hyperproliferative epithelial cell conditions, such as psoriasis, by administration of **thiazolidinediones** or 5'-aryl substituted thiazolidine derivatives is described. Appropriate chemical structures, synthetic reactions, formulations, routes of administration and dosages are included.
SUMM This invention relates to an additional medical use of **thiazolidinediones**, some of which are used in the treatment of **diabetes** and essential hypertension. These compounds are also useful for the treatment of psoriasis.
SUMM The invention provides methods for the treatment of psoriasis by effective dosages of thiazolidine derivatives known as **thiazolidinediones**. These compounds can also be used according to the invention to treat other disorders involving epidermal or epithelial cell proliferation.. . .
SUMM The **thiazolidinediones** have the advantage over conventional therapy of targeting the problem of psoriatic epidermal hyperplasia without disrupting the immune system, predisposing. . .
SUMM In human keratinocytes proliferating in culture, according to the invention, the **thiazolidinedione** ciglitazone caused a dose-dependent inhibition of keratinocyte cell growth. Based on the discovery that **thiazolidinediones** have a potent ability to attenuate proliferation of human keratinocytes, the invention includes the novel approach of using these agents. . .
DETD . . . psoriasis. The active ingredients of the compositions are well-known compounds which are generally described as 5'-aryl substituted thiazolidine derivatives or **thiazolidinediones**. These compounds are conventionally known for the treatment of **diabetes**. Particular examples are ciglitazone, pioglitazone (also known as AD-4833 and U-72107E), englitazone (also known as CP-68,722), and troglitazone (also know. . .
DETD . . . the Pancreatic Islets of Ob/Ob Mice, Metabolism, 37:276-280 (1988); and Chang, A. Y. et al., Ciglitazone, A New Hypoglycemic Agent, **Diabetes** 32:830-838 (1983).
DETD **Thiazolidinediones** conform to the following structural formula I: ##STR1## where variable ring substituents are defined below. A is H or methyl;
DETD 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-**thiazolidinedione** (commonly called pioglitazone);
DETD 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzoyl-2,4-**thiazolidinedione**.
DETD 5-{4-[2-(5-methyl-4-phenyl-2-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione**; and,
DETD 5-[4-(4-phenyl-2-thiazolylmethoxy)benzyl]-2,4-**thiazolidinedione**

.

DETD 5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione**
;

DETD 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-
thiazolidinedione; and,

DETD 5-{4-[2-(5-bromomethyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-
thiazolidinedione.

DETD 5-{4-[2-(5-ethyl-2-pyridyl)-2-hydroxyethoxy]benzyl}-2,4-
thiazolidinedione; and,

DETD 5-{4-[2-hydroxy-2-(6-methyl-2-pyridyl)ethoxy]benzyl}-2,4-
thiazolidinedione.

DETD The **thiazolidinedione** may be further selected from compounds wherein Y and Z are oxo and R.sub.1 is selected from compounds of the. . .

DETD The **thiazolidinedione** may be further selected from compounds wherein Y and Z are oxo and R.sub.1 is selected from compounds of the. . .

DETD . . . of reaction 1) together with Raney nickel alloy in aqueous formic acid. The product of reaction 2) reacts with the **thiazolidinedione** ring in a suitable solvent-base system. Suitable solvents include short chain alcohols, dimethyl-formamide, dimethylsulfoxide, sulfolane, acetonitrile, dioxane, dimethoxyethane or acetic. . .

DETD The **thiazolidinedione** ring reactant in step 3) is made according to the procedure detailed in part A above.

DETD . . . on the cyclohexane ring may be converted to the corresponding hydroxyl compounds by reduction. Preferable oxidizing agents are of the **chromium** trioxide species (e.g. Jones' reagent, **chromium** trioxide-pyridine) and preferable reducing agents are sodium borohydride and aluminum isopropoxide-isopropanol.

DETD In the first step of the above synthetic scheme, approximately equimolar amounts of the carbonyl reactant and the **thiazolidinedione** are heated in the presence of a mild base to provide the olefin product. While this step may be carried. . .

DETD In a typical reaction, the aldehyde or ketone starting material and **thiazolidinedione** are combined in approximately equimolar amounts with a molar excess, preferably a 2-14 fold molar excess, of anhydrous sodium acetate. . .

DETD An efficient one-step route to the sulfonyl-2,4-
thiazolidinediones employed a selective C-5 sulfonylation of dilithio-2,4-**thiazolidinedione** upon treatment with a sulfonyl chloride is presented (Scheme I). See Zask, et al., J. Med. Chem. 33:1418-1423 (1990), from. . . formula XII are taken and which is incorporated herein by reference. The dianion was readily prepared by the treatment of 2,4-**thiazolidinedione** with 2 equivalents of n-butyllithium. An alternative two-step sequence utilized a base-mediated coupling of a thiol with 5-bromo-2,4-
thiazolidinedione to provide the 5-thio intermediate, which was oxidized to the sulfone with an excess of hydrogen peroxide in acetic acid. . .

DETD The requisite 5-bromo-2,4-**thiazolidinedione** was obtained by bromination of 2,4-**thiazolidinedione** with bromine in acetic acid. In an analogous reaction, coupling of 2-naphthol with the **thiazolidinedione** in the presence of base gave the corresponding ether. Selective oxidation of the sulfide to the corresponding sulfoxide was effected. . .

DETD Selective N-methylation of the 2,4-**thiazolidinedione** ring was accomplished by treatment of naphthalene sulfone analogue with equimolar amounts of sodium hydride and iodomethane. Dimethylation of the. . . upon treatment with excess potassium carbonate and iodomethane. The C-5 methyl analogue was synthesized by preparation of the dianion of 5-methyl-2,4-**thiazolidinedione** followed by treatment with

1-naphthalenesolfonyl chloride.

DETD . . . to the 4-alkoxyphenyl sulfone analogue bearing the lipophilic alkoxy group found in ciglitazone utilized a nucleophilic displacement of fluoride from 5-[(fluoro-phenyl)sulfonyl]-2,4-**thiazolidinedione** by the alkoxide of (1-methylcyclohexyl)methanol (Scheme II). Treatment of the **thiazolidinedione** with (1-methylcyclohexyl)methanol in dimethyl-formamide in the presence of sodium hydride gave the desired analogue.

DETD Method A. 5-[(Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione**. To a stirred solution of 2,4-**thiazolidinedione** (5.5 g, 47 mmol) in tetrahydrofuran (THF) (275 mL) at -78.degree. C. under nitrogen was added n-butyllithium (62 mL, 99. . . sulfate) and then concentrated to give an oil, which was purified by chromatography (acid-washed silica gel, 10:1 chloroform/acetonitrile) to give 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione** (7.6 g, 42% yield): mp 189.degree.-190.degree. C. (acetonitrile/chloroform): .sup.1 H NMR (DMSO-d.sub.6, 200 MHz) .delta.6.60 (s, 1H, CH, exchanges with. . .

DETD Method B. 5-[(1-Bromo-2-naphthalenyl)thio]-2,4-**thiazolidinedione**. A solution of 5-bromo-2,4-**thiazolidinedione** (2.54 g, 13 mmol) and 1-bromo-2-mercaptonaphthalene (2.91 g, 13 mmol) in THF (100 mL) under nitrogen at -78.degree. C. was. . . (magnesium sulfate) and concentrated to give a yellow oil (5.27 g). Chromatography of this material (acid-washed silica gel, chloroform) gave 5-[(1-Bromo-2-naphthalenyl)thio]-2,4-**thiazolidinedione** (3.68 g, 83% yield): mp 128.degree.-129.degree. C. (hexane/ethyl acetate); .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta.6.42 (s, 1H, CH), 7.6-8.2. . .

DETD Method C. 5-(2-Naphthalenylsulfonyl)-2,4-**thiazolidinedione**. To a solution of 5-(2-thianaphthalenyl)-2,4-**thiazolidinedione** (2.5 g, 9.1 mmol) in acetic acid (100 mL) at 60.degree. C. was added 30% aqueous hydrogen peroxide (10 mL,. . . gel, 70:30 methanol/water) to give 2 as a foam (1.7 g, 62% yield). Crystallization from hexane/chloroform/methanol gave white needles of 5-(2-Naphthalenylsulfonyl)-2,4-**thiazolidinedione** (1.31 g, 47% yield): mp 196.degree.-197.degree. C.; .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta.6.75 (s, 1H CH, exchanges with D.sub.2. . .

DETD 5-Bromo-2,4-**thiazolidinedione**. To a solution of 2,4-**thiazolidinedione** (100 g, 0.885 mol) in acetic acid (250 mL) at 85.degree. C. was added bromine (42.7 mL, 0.885 mol) dropwise. . . was filtered through a short column of silica gel (8:1 chloroform/acetonitrile). The resulting oil was triturated with hexane to give 5-Bromo-2,4-**thiazolidinedione** as a white powder (95.0 g, 57% yield): mp 61.degree.-62.degree. C.; .sup.1 H NMR (acetone-d.sub.6, 200 MHz) .delta.6.41 (s, 1H,. . .

DETD 5-(2-Naphthalenyloxy)-2,4-**thiazolidinedione**. By a procedure similar to that of method B, a solution of 2-naphthol (5.0 g, 35 mmol) and 5-bromo-2,4-**thiazolidinedione** (6.8 g, 35 mmol) in THF (200 mL) was treated with lithium bis(tri-methylsilyl)amide (76 mL, 76 mmol, 1.0M in THF) to give, after chromatography (acid-washed silica gel, chloroform/acetonitrile), 5-(2-Naphthalenyloxy)-2,4-**thiazolidinedione** (2.8 g, 31% yield): mp 221.degree.-222.degree. C. (acetone/ethyl acetate); .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta.6.52 (s, 1H, OCH), 7.1-8.0. . .

DETD 5-(2-Naphthalenylsulfinyl)-2,4-**thiazolidinedione**. To a solution of 5-(2-thianaphthalenyl)-2,4-**thiazolidinedione** (1.0 g, 3.6 mmol) in dichloromethane (100 mL) was added m-chloroperbenzoic acid (0.74 g, 85%, 3.6 mmol) portionwise over 30. . . solid was washed repeatedly with hot carbon tetrachloride to remove m-chlorobenzoic acid. Recrystallization of the remaining solid (1.1 g) gave 5-(2-Naphthalenylsulfinyl)-2,4-**thiazolidinedione** as a 3:1 mixture of diastereomers (0.55 g, 52% yield): mp 157.degree.-158.degree.

C. (acetonitrile/carbon tetrachloride); .sup.1 H NMR (DMSO-d.sub.6, 400. . .

DETD 5-[[4-[(1-Methylcyclohexyl)methoxy]phenyl]sulfonyl]-2,4-**thiazolidinedione**. Sodium hydride (3.17 g, 66.1 mmol, 50% in oil) was added to a solution of (1-methylcyclohexl)methanol (8.47 g, 66.1 mmol) in dimethylformamide (30 mL). The mixture was heated to 55.degree. C. for 30 minutes. A solution of 5-[(4-fluorophenyl)sulfonyl]-2,4-**thiazolidinedione** (1.82 g, 6.61 mmol) in dimethylformamide (20 mL) was then added. After 3 hours at 55.degree. C., the reaction mixture. . . The resulting white foam (1.31 g) was rechromatographed (acid-washed silica gel, chloroform) and then recrystallized from hexane/ethyl acetate/ether to give 5-[[4-[(1-Methylcyclohexyl)methoxy]phenyl]sulfonyl]-2,4-**thiazolidinedione** as a white powder (0.97 g, 38% yield) mp 174.degree.-175.degree. C.; .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta.1.00 (s, 3H,. . .

DETD 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3-methyl-2,4-**thiazolidinedione**. To a solution of 5-[(Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione** (2.0 g, 5.2 mmol) in THF/dimethylformamide (1:1 40 mL) at 25.degree. C. under nitrogen was added sodium hydride (0.25 g,. . . phase was dried (magnesium sulfate) and concentrated to give crude product. Chromatography (silica gel, chloroform) and recrystallization (2.times. chloroform/ether) gave 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3-methyl-2,4-**thiazolidinedione** (520 mg, 25% yield): mp 150.degree.151.degree. C. .sup.1 H NMR (CDCl.sub.3, 400 MHz) .delta.3.03 (s, 3H, CH.sub.3), 5.59 (s, 1H,. . .

DETD 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3,5-dimethyl-2,4-**thiazolidinedione**. To a solution of 5-[(Bromo-1-naphthalenyl)sulfonyl]-2,4-**thiazolidinedione** (1.1 g, 2.9 mmol) in acetone (50 mL) at 25.degree. C. was added anhydrous potassium carbonate (3.9 g, 29 mmol). . . the mixture was filtered and the filtrate concentrated. Purification by chromatography (acid-washed silica gel, carboetetrachloride/chloroform) followed by recrystallization (chloroform/hexane/exane) gave 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3,5-dimethyl-2,4-**thiazolidinedione** (0.69 g, 59% yield): mp 160.degree.-161.degree. C. .sup.1 H NMR (CDCl.sub.3, 400 MHz) .delta.2.10 (s, 3H, CH.sub.3), 2.69 (s, 3H,. . .

DETD 5-[(6-Hydroxyl-2-naphthalenyl)thio]- 2,4-**thiazolidinedione**. Potassium hydroxide (2.47 g, 44.0 mmol) was added to a suspension of 5-[(6-ethoxycarbonyloxy-2-naphthalenyl)thio]-2,4-**thiazolidinedione** (8.0 g, 22 mmol) in methanol (50 mL) at 25.degree. C. After 30 minutes, the resulting solution was acidified to. . . pH=1 with and then extracted with ethyl acetate (3.times.). The combined extracts were dried (magnesium sulfate) and concentrated to give 5-[(6-Hydroxyl-2-naphthalenyl)thio]-2,4-**thiazolidinedione** as a powder (6.4 g, 99% yield): mp 182.degree.-183.degree. C. (chloroform/ethyl acetate); .sup.1 H NMR (DMSO-d.sub.6, 400 MHz) .delta.6.07 (s,. . .

DETD A preferred way to practice the invention is to apply the **thiazolidinedione** compound, in a cream or oil based carrier, directly to the psoriatic lesions. Typically, the concentration of therapeutic compound in. . . cream or oil is 1-2%. Alternatively, an aerosol can be used topically. These compounds can also be orally administered. The **thiazolidinedione** compound trogitazone (Sankyo's CS-045 and Parke-Davis' CI-991), is an example of a **thiazolidinedione** that can be used in this fashion.

CLM What is claimed is:

11. A method of claim 2 wherein the **thiazolidinedione** is selected from compounds where X is a bond and R.sub.1 is of formula IX ##STR64## where n is an. . .

12. A method of claim 2 wherein the **thiazolidinedione** is selected from compounds where R.sub.1 is of the formula XI ##STR65##

wherein the broken line is a bond or. . .
AN 97:3862 USPATFULL|
TI Thiazolidine derivatives for the treatment of psoriasis|
IN Kurtz, Theodore W., Mill Valley, CA, United States
Pershadsingh, Harrihar A., Bakersfield, CA, United States
PA Regents of the University of California, Oakland, CA, United States (U.S. corporation)
PI US 5594015 19970114 <--
AI US 1994-263446 19940622 (8)
DT Utility|
FS Granted|
EXNAM Primary Examiner: Dees, Jos e G.; Assistant Examiner: Frazier, Barbara S.|
LREP Townsend and Townsend and Crew|
CLMN Number of Claims: 23|
ECL Exemplary Claim: 1|
DRWN 15 Drawing Figure(s); 8 Drawing Page(s)|
LN.CNT 1802|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 7 OF 13 USPATFULL
PI US 5498621 19960312 <--
SUMM In spite of the early discovery of insulin and its subsequent wide-spread use in the treatment of **diabetes**, and the later discovery and use of sulfonylureas (e.g. chlorpropamide, tolbutamide, acetohexamide, tolazamide) and biguanides (e.g. phenformin) as oral hypoglycemic agents, the treatment of **diabetes** remains less than satisfactory. The use of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type I **diabetes**, insulin dependent **diabetes** mellitus), requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of. . . causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose or coma, or even death. Treatment of non-insulin dependent **diabetes** mellitus (Type II **diabetes**) usually consists of a combination of diet, exercise, oral agents, e.g., sulfonylureas, and in more severe cases, insulin. However, the. . .
SUMM Schnur, U.S. Pat. No. 4,617,312 discloses hypoglycemic **thiazolidinediones** of the formula ##STR3## where R.sup.c is lower alkyl, is F, Cl or Br, and y.sup.a is X.sup.a is hydrogen,. . .
SUMM Eggler et al., U.S. Patent 4,703,05discloses hypoglycemic **thiazolidinediones** of the formula ##STR6## where the dotted line represents an optional bond, R.sup.f is H, methyl or ethyl, X.sup.b is. . .
SUMM Meguro et al., U.S. Pat. No. 4,725,610 disclose a series of hypoglycemic **thiazolidinediones** of the formula ##STR7##
SUMM EP 283,035A and EP 299,620A describe benzoxazole and benzofuran linked **thiazolidinediones** as antidiabetic agents.
DETD . . . solution of 1.0 g of 2-phenyl-4-hydroxyethyl5-methyloxazole in 20 ml of acetone was added a solution consisting of 1 g of **chromium** trioxide, 0.9 ml of concentrated sulfuric acid and 4 ml of water and the reaction stirred at room temperature for. . .
AN 96:21101 USPATFULL
TI Oxazolidinedione hypoglycemic agents
IN Dow, Robert L., Waterford, CT, United States
Hulin, Bernard, Essex, CT, United States
Clark, David A., East Lyme, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 5498621 19960312 <--
AI US 1994-289612 19940812 (8)
RLI Continuation of Ser. No. US 1992-855038, filed on 1 May 1992, now

abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Daus, Donald G.
LREP Richardson, Peter C., Benson, Gregg C., Ronau, Robert T.
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1103
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 8 OF 13 USPATFULL
TI **Thiazolidinedione** derivatives, production and use thereof
PI US 5441971 19950815 <--
WO 9218501 19921029
AB A **thiazolidinedione** compound of the formula ##STR1## wherein X,Q are as defined in the specification. The compounds are used for treating **diabetes**.
SUMM The present invention relates to novel **thiazolidinedione** derivatives having hypoglycemic and hypolipidemic activities, the production thereof and a pharmaceutical composition for treating **diabetes** containing them.
SUMM Various biguanide compounds and sulfonylurea compounds have been used as agents for treating **diabetes**. However, at present, biguanide compounds are scarcely used because they cause lactic acidosis. Although sulfonylurea compounds have strong hypoglycemic activity,. . .
SUMM . . . studied to find out compounds having hypoglycemic activity without the above drawbacks. As a result, it has been found novel **thiazolidinedione** derivatives having excellent hypoglycemic and hypolipidemic activities. Thus, the present invention have been completed.
SUMM According to the present invention, there is provided a **thiazolidinedione** derivative of the general formula (I): ##STR2## wherein X is --CH.sub.2 -- or --CO--, Q is CH.sub.3 CO--, CH.sub.3 CH(OR)--. . .
SUMM The present invention also provide a pharmaceutical composition;for treating **diabetes** comprising as an effective component the **thiazolidinedione** derivative of the general formula (I), a pharmacologically acceptable salt thereof or a pure stereoisomeric form thereof.
SUMM The **thiazolidinedione** derivative of the general formula (I) (hereinafter referred to as the compound (I)) possesses an acidic nitrogen atom in the. . .
SUMM 5-[4-[2-(5-acetyl-2-pyridyl)ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-acetoxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-propionyloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-butyryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-isobutyryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-valeryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-isovaleryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-pivaloyloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-[2-[5-(1-benzoyloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-

thiazolidinedione;

SUMM 5-[4-[2-(5-carboxymethyl-2-pyridyl)ethoxy]benzyl]-2,4-**thiazolidinedione;** and

SUMM 5-[4-[2-(5-ethyl-2-pyridyl)-2-oxoethoxy]benzyl]-2,4-**thiazolidinedione.**

SUMM . . . was observed. Therefore, the compound (I), its pharmacologically acceptable salt or pure stereoisomeric form can be used for treatment of **diabetes** of mammals including man as it is or by combining with a known pharmacologically acceptable carrier, excipient, filler and the. . .

SUMM . . . be carried out according to a known method. Examples thereof include oxidation with manganese dioxide, oxidation with chromic acid (e.g., **chromium** (IV) oxide-pyridine complex), oxidation with dimethyl sulfoxide and the like [see Shin Jikken Kagaku Koza, Vol. 15 (I-1), (I-2), edited. . .

SUMM . . . (I) of the present invention has excellent hypoglycemic and hypolipidemic activities, and is useful for a therapeutic agent for treating **diabetes**, hyperlipidemia and the like.

SUMM As described hereinabove, according to the present invention, there is provided novel **thiazolidinedione** derivatives or salts thereof which have excellent hypoglycemic and hypolipidemic activities without causing lactic acidosis and hypoglycemia.

DETD . . . The oily residue thus obtained was subjected to silica gel column chromatography. A fraction eluted with chloroform-methanol (40:1, v/v) gave 5-[4-[2-[5-(1-hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** (14.8 g, yield: 66%). This crude compound was recrystallized from ethanol to obtain colorless prisms, m.p. 155.degree.-156.degree. C.

DETD Acetic anhydride (25 ml) was added to a solution of 5-[4-[2-[5-(1-hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** (8.7 g) in dimethyl sulfoxide (100 ml). The mixture was allowed to stand at room temperature for 4 days. The. . . reduced pressure. The oily residue was subjected to silica gel column chromatography. A fraction eluted with chloroform-methanol (100:1, v/v) gave 5-[4-[2-(5-acetyl-2-pyridyl)ethoxy]benzyl]-2,4-**thiazolidinedione**. This compound was recrystallized from ethanol to obtain colorless prisms, m.p. 114.degree.-115.degree. C.

DETD 5-[4-[2-[5-(1-Hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** (0.3 g) was dissolved in hydrogen chloride-ethanol (25%, 1 ml). The solution was stirred at room temperature for 30 minutes and precipitated crystals were filtered off. The crystals were recrystallized from ethanol to obtain 5-[4-[2-[5-(1-hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** hydrochloride (0.21 g, yield: 62%) as colorless prisms, m.p. 212.degree.-213.degree. C.

DETD A mixture of 5-[4-[2-[5-(1-hydroxyethyl)-2-pyridyl]benzyl]-2,4-**thiazolidinedione**.1/4 ethanol (384 mg), acetic anhydride (0.5 ml) and pyridine (5 ml) was stirred at room temperature for 12 hours. After. . . concentrated under reduced pressure and the remaining crystals were filtered off. The crystals were recrystallized from ethyl acetate-hexane to obtain 5-[4-[2-[5-(1-acetoxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** (345 mg, yield: 83%) as colorless prisms, m.p. 143.degree.-144.degree. C.

DETD . . . The resulting solution was washed with water and dried over magnesium sulfate and the solvent was distilled off to obtain 5-[4-[2-(5-carboxymethyl-2-pyridyl)ethoxy]benzyl]-2,4-**thiazolidinedione** (1.9 g, yield: 79%). This compound was recrystallized from ethanol to obtain colorless prisms, m.p. 144.degree.-145.degree. C.

DETD A mixture of 5-[4-[2-(5-ethyl-2-pyridyl)-2-hydroxyethoxy]benzyl]-2,4-**thiazolidinedione**. 1/2 C.sub.2 H.sub.5 OH (396 mg), acetic anhydride (1.5 ml) and dimethylsulfoxide (4 ml) was stirred at room

temperature for. . . was distilled off. The oily residue was subjected to silica gel chromatography. A fraction eluted with chloroform-methanol (100:1, v/v) gave 5-[4-[2-(5-ethyl-2-pyridyl)-2-oxoethoxy]benzyl]-2,4-**thiazolidinedione** (75 mg, yield: 20%). This was recrystallized from ethyl acetate-hexane to obtain colorless prisms, m.p. 148.degree.-149.degree. C.

DETD

(1)	5-[4-[2-[5-(1-hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** 1/4 ethanol solvate	100	g
(2)	Lactose	50	g
(3)	Corn starch	15	g
(4)	Calcium carboxymethylcellulose	44	g
(5)	Magnesium stearate	1	g

1000 tablets. . .

CLM What is claimed is:

1. A **thiazolidinedione** compound of the formula (I): ##STR10## wherein X is --CH.sub.2 -- or --CO--; wherein Q is CH.sub.3 CO--, CH.sub.3 CH(OR)--,. . .

2. A **thiazolidinedione** compound according to claim 1, wherein X is --CH.sub.2 -- or --CO--, Q is CH.sub.3 CO-- or CH.sub.3 CH(OR)--, when. . .

3. A **thiazolidinedione** compound according to claim 1, wherein X is --CH.sub.2 -- and Q is CH.sub.3 CH(OH)-- or --CH.sub.2 COOH.

4. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-(5-acetyl-2-pyridyl)ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

5. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

6. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-acetoxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

7. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-propionyloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

8. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-butyryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

9. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-isobutyryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

10. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-valeryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

11. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-isovaleryloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

12. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-[5-(1-pivaloyloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-

thiazolidinedione or its salt.

13. The **thiazolidinedione** compound according to claim 1 Which is 5-[4-[2-(5-carboxymethyl-2-pyridyl)ethoxy] benzyl]-2,4-**thiazolidinedione** or its salt.

14. The **thiazolidinedione** compound according to claim 1 which is 5-[4-[2-(5-ethyl-2-pyridyl)-2-oxoethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

15. The **thiazolidinedione** compound which is according to claim 1 which is 5-[4-[2-[5-(1-benzoyloxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-**thiazolidinedione** or its salt.

16. A pharmaceutical composition for treating **diabetes** comprising the **thiazolidinedione** derivative according to claim 1, and a pharmacologically acceptable carrier, excipient or diluent.

17. A pharmaceutical composition for treating **diabetes** comprising the **thiazolidinedione** derivative according to claim 2, and a pharmacologically acceptable carrier, excipient or diluent.

18. A pharmaceutical composition for treating **diabetes** comprising the **thiazolidinedione** derivative according to claim 3, and a pharmacologically acceptable carrier, excipient or diluent.

19. A method for treating **diabetes** which comprising administering an effective amount of the **thiazolidinedione** derivative according to claim 1, optionally together with a pharmacologically acceptable carrier, excipient or diluent to a patient requiring such. . .

20. A method for treating **diabetes** which comprising administering an effective amount of the **thiazolidinedione** derivatives according to claim 2, optionally together with a pharmacologically acceptable carrier, excipient or diluent to a patient requiring such. . .

21. A method for treating **diabetes** which comprising administering an effective amount of the **thiazolidinedione** derivatives according to claim 3, optionally together with a pharmacologically acceptable carrier, excipient or diluent to a patient requiring such. . .

AN 95:73652 USPATFULL|
TI **Thiazolidinedione** derivatives, production and use thereof|
IN Sohda, Takashi, Osaka, Japan
Ikeda, Hitoshi, Osaka, Japan
Greenfield, John C., Richland, MI, United States
Colca, Jerry R., Texas Township, MI, United States
Petzold, Edgar N., Plainwell, MI, United States
PA The Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)
Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 5441971 19950815 <--
WO 9218501 19921029
AI US 1993-137135 19931012 (8)
WO 1992-US2566 19920406
19931012 PCT 371 date
19931012 PCT 102(e) date
PRAI JP 1991-78836 19910411
DT Utility|
FS Granted|
EXNAM Primary Examiner: Fan, Jane|
LREP Welch, Lawrence T.|
CLMN Number of Claims: 21|

ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 696|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 9 OF 13 USPATFULL
PI US 5070100 19911203 <--
AB . . . containing a secondary amide, and the pharmaceutically acceptable salts thereof. These compounds are useful, inter alia in the treatment of **diabetes**. Also disclosed are processes for the preparation of such compounds; pharmaceutical compositions comprising such compounds; and methods of treatment comprising administering such compounds and compositions when indicated for, inter alia, long term, prophylactic treatment of the **diabetes** syndrome. A particularly preferred class of compounds comprise difluoro-dialkoxy substituted spiro-(9H-fluorene-9,4'-imidazolidine)-2,40 ,5-diones.
SUMM . . . reductase inhibitors such as 1,3-dioxo-1H-benz [d,e]-isoquinoline-2(3H)-acetic acid, and its derivatives, are useful as inhibitors of aldose reductase and alleviators of **diabetes** mellitus complications. Spiro-[chroman-4,4'-imidazolidine]-2',5'-dione and spiro-[imidazolidine-4,4'-thiochroman]-2,5-dione and their derivatives, disclosed in U.S. Pat. Nos. 4,130,714 and 4,209,630, are also indicated as. . .
SUMM . . . related spiro-heterocyclic analogs, and methods for their preparation, which compounds are useful as inhibitors of aldose reductase and alleviators of **diabetes** mellitus complications.
SUMM . . . still further object of the invention is to provide pharmaceutical compositions and methods for inhibiting aldoreductase and the treatment of **diabetes** mellitus wherein the active ingredient comprises a spiro-tricyclicaromatic succinimide derivative or spiro-heterocyclic analog.
SUMM The present invention is concerned with novel spiro-tricyclicaromatic succinimide derivatives and relates spiro-heterocyclic analogs such as spiro-tricyclicaromatic-**thiazolidinedione**, -imidazolidinedione, and -oxazolidinedione derivatives. The invention is also concerned with methods for preparation of these compounds, and methods for treatment. . .
SUMM . . . from hyperglycemia or hypergalactocemia. Hyperglycemia is associated with the complications of neuropathy, retinopathy, cataract, glaucoma, and impaired wound healing in **diabetes** mellitus patients.
SUMM . . . vascular tissues. Effective aldose reductase inhibitor chemotherapy prevents, improves, or delays the onset, duration or expression of certain sequelae of **diabetes** mellitus which include ocular sequelae (e.g., cataract and retinopathy), kidney damage (nephropathy), neurological dysfunction (e.g., peripheral sensory neuropathy), vascular disease. . .
SUMM . . . fluorene or fluorene-like aromatic ring system spiro-coupled to a five-membered imide (or cyclic secondary amide) ring such as succinimide, hydantoin, **thiazolidinedione** or oxazolidinedione. These spirocyclic derivatives of the various tricycles each contain a polarizable and hydrogen-bondable secondary amide, also called imide,. . .
SUMM . . . direct aromatic halogenations may be conveniently performed after the tricyclic aromatic is spiro-imide derivatized, e.g., converted to the hydantoin or **thiazolidinedione**. In addition, certain labile protecting groups may be employed as is known and practiced in the art.
SUMM . . . appropriate fluorene and heterocyclic analogs of fluorene derivatives of Formula III, wherein A and B are previously defined. For example, spiro-**thiazolidinedione** derivative (26) is prepared from 5H-indeno[1,2-b]pyridine: ##STR13## Likewise, the spiro-

thiazolidinedione of example (12) is prepared from its starting material 2-fluoro-9H-fluorene: ##STR14## The synthesis of a spiro-**thiazolidinedione** from the corresponding tricyclic fluorene or heterocyclic fluorene derivative is a multi-stepped synthesis as depicted in Example IV. The first. . . ##STR20## Hydrolysis of the spiro-aminothiazolone in an acidic aqueous alcoholic solution such as concentrated hydrochloric acid in methanol yields the spiro-**thiazolidinedione**, e.g., spiro-(2-fluoro-9H-fluorene-9,5'-thiazolidine)-2',4'-dione. ##STR21## Reaction starting materials, tricyclic fluorene and tricyclic heterocyclic flourene derivatives of Formula III, are prepared by methods. . .

SUMM . . . heterotricyclic analogs of fluorene of Formula III, wherein A and B are previously defined. The synthesis of the spiro-oxazolidinediones and spiro-**thiazolidinediones** (see II) generally have common synthetic intermediates. For example, spiro-tricyclicoxazolidinedione derivative (6) is prepared from the tricyclic .alpha.-hydroxy ester, 2-fluoro-9-hydroxy-9H-fluorene-9-carboxylic acid methyl ester, which is an intermediate in the synthesis of spiro-tricyclic-**thiazolidinedione** (12). Reaction of the .alpha.-hydroxy ester with 1 to 2 (preferably 1.1) equivalents of urea and 1 to 2 (preferably. . .

SUMM . . . analogs of fluorene of Formula III, wherein A and B are previously defined. The synthesis of the spiro-tricyclicsuccinimides, spiro-oxazolidinediones and spiro-**thiazolidinediones** generally have common synthetic intermediates. For example, spiro-tricyclicsuccinimide derivatives (20) and (21) are prepared from the tricyclic acid esters, 9H-fluorene-9-carboxylic. . .

SUMM The novel spiro-tricyclic-imidazolidinediones, -**thiazolidinediones**, -oxazolidinediones and -succinimides may be further derivatized according to the following.

SUMM . . . acid and 60% sulfuric acid) of the spiro-cyclic derivatives, especially spiro-hydantoin (see Example XI). After nitration of the selected spiro-tricyclic-imidazolidinediones, -**thiazolidinediones**, -oxazolidinediones and succinimides by methods well known and practiced in the art, the corresponding aromatic nitro group(s) of corresponding spiro-tricyclic. . .

SUMM c) Oxidation by selenium dioxide in a sealed vessel at 200.degree.-250.degree. C. when common oxidation procedures such as **chromium** trioxide in acetic acid are ineffective. See Arcus and Barnett, J. Chem. Soc. (1960) 2098.

SUMM The spiro-tricyclic-**thiazolidinedione**, -imidazolidinedione, -oxazolidinedione and -succinimide compounds of the present invention are weak acids. In addition, several examples, as cited in Example. . .

SUMM . . . sodium, potassium, calcium, magnesium, etc. These pharmacologically acceptable nontoxic salts can be prepared by treating the aforementioned acidic specie, e.g., spiro-**thiazolidinedione**, with aqueous metallic hydroxide solution, and then evaporating the resulting solution, preferably at reduced pressure, to dryness. Alternatively, where indicated,. . .

SUMM As previously indicated, the spiro-tricyclic-**thiazolidinedione**, -imidazolidinedione, -oxazolidinedione and -succinimide compounds of this invention are all readily adapted to therapeutic use as aldose reductase inhibitors for. . .

SUMM . . . of the clinician, long term, prophylactic administration of the compounds of the present invention is generally indicated on diagnosis of **diabetes** mellitus and/or neuropathy and/or retinopathy and/or vasculopathy and/or cataract and/or impaired wound healing and/or nephropathy and/or hyperglyceamia.

SUMM . . . e.g., 6-fluoro-8H-indeno[2,1-b]thiophen-8-carboxylic acid methyl ester. The ester is utilized according to Methods II, III and IV to yield the corresponding spiro-**thiazolidinedione**,

spiro-oxazolidine-dione and spiro-succinimide such as spiro-(6-fluoro-8H-indeno[2,1-b]thiophen-8,5'-thiazolidine)-2',4'-dione, spiro-(6-fluoro-8H-indeno-8,5'-oxazolidine)-2,4'-dione and spiro-(6-fluoro-8H-indeno[2,1-b]thiophen-8,3'-succinimide) respectively.

SUMM . . . e.g., 6-chloro-4H-indeno[1,2-b]thiophen-4-carboxylic acid methyl ester. The ester is utilized according to Methods II, III and IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide such as spiro-(6-chloro-4H-indeno[1,2-b]thiophen-4,5'-thiazolidine]-2',4'-dione, spiro-(6-chloro-4H-indeno[1,2-b]thiophen-4,5'-oxazolidine)-2',4'-dione and spiro-(6-chloro-4H-indeno[1,2-b]thiophen-4,3'-succinimide) respectively. The resulting spiro-derivatives may be further derivatized according to Method. . .

SUMM . . . (and optional derivatization according to Method V) and spiro-derivatization in accordance with Methods II, III and IV yields the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives respectively. These spiro-derivatives may be further derivatized according to Method VI.

SUMM . . . substrate 7H-cyclopenta[1,2-b:4,3-b']dithiophene is prepared according to the method of Wynberg and Kraak, J. Org. Chem., 29, 2455 (1964). The corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives are prepared according to Methods II-IV respectively. The 7-one derivative is prepared from the cyclopentadithiophene in. . .

SUMM . . . and 7H-cyclopenta[2,1-b:3,4-c']dithiophene are prepared according to the procedure of Wiersema and Wynberg, Tetrahedron, 24, 3381 (1968). From these, the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives are prepared according to Methods II-IV respectively. The corresponding 4H-cyclopenta[2,1-b:3,4-b']dithiophen-4-one, 7H-cyclopenta[1,2-b:3,4-b']dithiophen-7-one, 7H-cyclopenta[1,2-c:3,4c']dithiophen-7-one, 7H-cyclopenta[1,2-b:3,4-c']dithiophen-7-one and 7H-cyclopenta[2,1-b:3,4-c']dithiophen-7-one are. . .

SUMM . . . 9, 849 (1978) to yield the corresponding 5H-indeno[1,2-c]pyridine which is derivatized in accordance with Methods II-IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide respectively. The aforementioned spiro-derivatives may be further derivatized according to Method VI.

SUMM . . . accordance with Method V. The resulting indenopyridine or 2-azafluorene product is further derivatized according to Methods II-IV to yield the spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives. Oxidation of the indenopyridine to the corresponding ketone is accomplished by sodium dichromate or other oxidation. . .

SUMM . . . via the Schiemann reaction into 7-fluoro-9H-indeno[2,1-c]pyridine. This substrate, as above, can be transformed by Methods I-IV into spiro-(7-fluoro 9H-indeno[2,1-c]pyridin-9,4'-imidazolidine)-2',5'-dione, spiro-(7-fluoro 9H-indeno[2,1-c]pyridin-9,5'-**thiazolidinedione**)-2',4'-dione, spiro-(7-fluoro 9H-indeno[2,1-c]pyridin-9,5'-oxazolidine)-2,4'-dione and spiro-(7-fluoro 9H-indeno[2,1-c]pyridin-9,3'-succinimide).

SUMM . . . Wolff-Kishner reduction to yield corresponding 9H-indeno[2,1-b]pyridine which is then derivatized in accordance with Methods II, III and IV to yield spiro-**thiazolidinedione**, spiro-succinimide.

SUMM . . . e.g., 7-fluoro-1-azafluorene. The 9H-indeno[2,1-b]pyridine and its derivatives (e.g., 7-fluoro-9H-indeno[2,1-b]pyridine) are converted in accordance with Method II, III and IV into spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives. The 9H-indeno[2,1-b]pyridine is oxidized according to

general procedures cited in Method VII or potassium permanganate (Urbina,. . .

SUMM . . . the corresponding diazafluorene substrates such as 5H-cyclopenta[2,1-b:4,3-b']dipyridine. These diazafluorene substrates are derivatized according to Methods II-IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives.

SUMM . . . to Method V. The derivatized or underivatized 4H-indeno[1,2-b]furan according to Method II, III and IV is derivatized to the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide respectively.

SUMM . . . derivatized or underivatized heterocycle then may be further derivatized according to Method II, III or IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione or spiro-succinimide respectively. These spiro-derivatives in turn may be derivatized in accordance with Method VI.

SUMM . . . be further derivitized in accordance with Method V and according to Methods II, III and IV derivatized into the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimides respectively. These spiro derivatives in turn may be further derivatized according to Method VI. oxidation of the. . .

SUMM . . . H-thieno-pyrrolizines quantitatively. The resulting thieno[2,3-b]pyrrolizine and [2,3-b]pyrrolizine can be derivatived according to Methods II, III and IV into the corresponding spiro-**thiazolidinediones**, spiro-oxazolidinediones and spiro-succinimides, such as spiro-(thieno[3,2-b]pyrrolizin-4,5'-thiazolidine)2',4'-dione, spiro-(thieno[2,3-b]pyrrolizin4,5'-oxazolidine)-2',4'-dione and spiro-(thieno[3,2-b]pyrrolizin-4,3'-succinimide).

SUMM After spiro-derivatization the corresponding spiro-hydantoin, spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide products are obtained.

SUMM . . . to the spiro-hydantoin. Alternately the heterocycle may be derivatized in accordance with methods II, III and IV to the corresponding spiro-**thiazolidinedione**, spiro-oxazolindinedione and spiro-succinimide. These may be further derivatized in accordance with Method VI.

DETD . . . Calc. %C 67.40, %H 3.39; %N 5.24: meas. %C 67.46, %H 3.34, N 5.32. For the hydrolysis of 2-amino-4-thaizolones to **thiazolidinediones** using methanolic hydrogen chloride, see: Koltai, Tetrahedron (1973) 29, 2781.

DETD The product (50) can be derivatized in accordance with Methods II, III and IV into the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide.

DETD . . . moles of sodium hydroxide and then freeze-drying the mixture. In this way, the desired alkali metal salt of the spiro-hydantoin, spiro-**thiazolidinedione**, spiro-oxazolidinedione or spiro-succinimide can be prepared. In those cases where the aromatic substituents contain carboxylic acid moieties (e.g., isopropanoic acid. . .

DETD . . . containing 10, 25 and 200 mg of active ingredient, respectively, by merely using an appropriate quantity by weight of the spiro-**thiazolidinedione** in each case. Likewise other related examples of spiro-thiazoidinediones, spiro-imidazolidinediones, spiro-oxazolidinediones, spiro-succinimides and be formulated as tablets on a respective. . .

CLM What is claimed is:

3. A pharmaceutical composition for the treatment of complications of **diabetes** mellitus in humans comprising an effective amount of a compound of claim 1 and a pharmaceutical vehicle.

9. A pharmaceutical composition for the treatment of complications of

diabetes mellitus in humans comprising an effective amount of a compound of claim 8 and a pharmaceutical vehicle.

11. A method for the treatment of complications of **diabetes** mellitus in humans and animals comprising administering thereto a composition of claim 9.

AN 91:98403 USPATFULL|
TI Spiro-tricyclicaromatic succinimide derivatives|
IN York, Jr., Billie M., Crowley, TX, United States
PA Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)
PI US 5070100 19911203 <--
AI US 1989-402035 19890905 (7)
RLI Continuation-in-part of Ser. No. US 1987-94636, filed on 9 Sep 1987, now patented, Pat. No. US 4864028, issued on 5 Sep 1989 which is a continuation-in-part of Ser. No. US 1987-5859, filed on 21 Jan 1987, now abandoned which is a continuation of Ser. No. US 1985-776569, filed on 14 Aug 1985, now abandoned which is a continuation of Ser. No. US 1983-532168, filed on 14 Sep 1983, now patented, Pat. No. US 4537892
DT Utility|
FS Granted|
EXNAM Primary Examiner: Ford, John M.|
LREP Arno, James A., Brown, Gregg C., Price, Robert L.|
CLMN Number of Claims: 13|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 3120|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 10 OF 13 USPATFULL
PI US 5053420 19911001 <--
SUMM . . . Killer?, New Eng. J. Med. 320:733-734, and Reaven, G. M., 1988, Banting Lecture: Role of Insulin Resistance in Human Disease, **Diabetes** 37:1595-1607.
SUMM . . . the Pancreatic Islets of Ob/Ob Mice, Metabolism, 37:276-280; and, Chang, A. Y., et al., 1983, Ciglitazone, A New Hypoglycemic Agent, **Diabetes** 32:830-838.
SUMM 5-{4-[2-(5-methyl-4-phenyl-2-oxazoyl)ethoxy]benzyl}2,4-**thiazolidinedione**; and,
SUMM 5-[4-(4-phenyl-2-thiazolylmethoxy)benzyl]-2,4-**thiazolidinedione**.
SUMM 5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione**;
SUMM 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione**; and,
SUMM 5-{4-[2-(5-bromomethyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione**.
SUMM 5-{4-[2-(5-ethyl-2-pyridyl)-2-hydroxyethoxy]benzyl}2,4-**thiazolidinedione**; and,
SUMM 5-{4-[2-hydroxy-2-(6-methyl-2-pyridyl)ethoxy]benzyl}2,4-**thiazolidinedione**.
SUMM . . . and are generally described as 5'-Aryl Substituted thiazolidine derivatives. These compounds are known to be useful for the treatment of **diabetes**.
SUMM . . . of reaction 1) together with Raney nickel alloy in aqueous formic acid. The product of reaction 2) reacts with the **thiazolidinedione** ring in a suitable solvent-base system. Suitable solvents include short chain alcohols, dimethyl-formamide, dimethylsulfoxide, sulfolane, acetonitrile, dioxane, dimethoxyethane or acetic. . .
SUMM The **thiazolidinedione** ring reactant in step 3) is made

according to the procedure detailed in part A above.

SUMM . . . on the cyclohexane ring may be converted to the corresponding hydroxyl compounds by reduction. Preferable oxidizing agents are of the **chromium** trioxide species (e.g. Jones' reagent, **chromium** trioxide-pyridine) and preferable reducing agents are sodium borohydride and aluminum isopropoxide-isopropanol.

AN 91:79972 USPATFULL

TI Thiazolidine derivatives for the treatment of hypertension

IN Pershadsingh, Harrihar A., 2812 Burger St., Bakersfield, CA, United States 93305
Kurtz, Theodore W., 1251 Lattie La., Mill Valley, CA, United States 94941

PI US 5053420 19911001 <--

AI US 1989-421102 19891013 (7)

DT Utility

FS Granted

EXNAM Primary Examiner: Waddell, Frederick E.; Assistant Examiner: Criares, T. J.

LREP Townsend and Townsend

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 993

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 11 OF 13 USPATFULL

PI US 4864028 19890905 <--

AB . . . containing a secondary amide, and the pharmaceutically acceptable salts thereof. These compounds are useful, inter alia, in the treatment of **diabetes**. Also disclosed are processes for the preparation of such compounds; pharmaceutical compositions comprising such compounds; and methods of treatment comprising administering such compounds and compositions when indicated for, inter alia, long term, prophylactic treatment of the **diabetes** syndrome.

SUMM . . . aldose reductase inhibitors such as 1,3-dioxo-1H-benz[d,e]-isoquinoline-2-(3H)-acetic acid, and its derivatives, are useful as inhibitors of aldose reductase and alleviators of **diabetes** mellitus complications. Spiro-[chroman-4,4'-imidazolidine]-2',5'-dione and spiro-[imidazolidine-4,4'-thiochroman]-2,5-dione and their derivatives, disclosed in U.S. Pat. No. 4,130,714 and U.S. Pat. No. 4,209,630, are. . .

SUMM . . . related spiro-heterocyclic analogs, and methods for their preparation, which compounds are useful as inhibitors of aldose reductase and alleviators of **diabetes** mellitus complications.

SUMM . . . further object of the invention is to provide pharmaceutical compositions and methods for inhibiting aldose reductase and the treatment of **diabetes** mellitus wherein the active ingredient comprises a spiro-tricyclicaromatic succinimide derivative or spiro-heterocyclic analog.

SUMM The present invention is concerned with novel spiro-tricyclicaromatic succinimide derivatives and related spiro-heterocyclic analogs such as spiro-tricyclicaromatic-**thiazolidinedione**, -imidazolidinedione, and -oxazolidinedione derivatives. The invention is also concerned with methods for preparation of these compounds, and methods for treatment. . .

SUMM . . . hyperglycemia or hypergalactocemia. Hyperglycemia is associated with the complications of neuropathy, nephropathy, retinopathy, cataract, glaucoma, and impaired wound healing in **diabetes** mellitus patients.

SUMM . . . vascular tissues. Effective aldose reductase inhibitor chemotherapy prevents, improves, or delays the onset, duration, or expression of certain sequalae of **diabetes** mellitus which

include ocular sequalae (e.g., cataract and retinopathy), kidney damage (nephropathy), neurological dysfunction (e.g., peripheral sensory neuropathy), vascular disease. . .

SUMM . . . fluorene or fluorene-like aromatic ring system spiro-coupled to a five-membered imide (or cyclic secondary amide) ring such as succinimide, hydantoin, **thiazolidinedione** or oxazolidinedione. These spirocyclic derivatives of the various tricycles each contain a polarizable and hydrogen-bondable secondary amide, also called imide,. . .

SUMM . . . direct aromatic halogenations may be conveniently performed after the tricyclic aromatic is spiro-imide derivatized, e.g., converted to the hydantoin or **thiazolidinedione**. In addition, certain labile protecting groups may be employed as is known and practiced in the art.

SUMM . . . appropriate fluorene and heterocyclic analogs of fluorene derivatives of Formula III, wherein A and B are previously defined. For example, spiro-**thiazolidinedione** derivative (26) is prepared from 5H-indeno[1,2-b]pyridine: ##STR13## Likewise, the spiro-**thiazolidinedione** of example (12) is prepared from its starting material 2-fluoro-9H-fluorene: ##STR14##

SUMM The synthesis of a spiro-**thiazolidinedione** from the corresponding tricyclic fluorene or heterocyclic fluorene derivative is a multistepped synthesis as depicted in Example IV. The first. . .

SUMM . . . ##STR20## Hydrolysis of the spiro-aminothiazolone in an acidic aqueous alcoholic solution such as concentrated hydrochloric acid in methanol yields the spiro-**thiazolidinedione**, e.g., spiro-(2-fluoro-9H-fluorene-9,5'-thiazolidine)-2',4'-dione. ##STR21##

SUMM . . . heterotricyclic analogs of fluorene of Formula III, wherein A and B are previously defined. The synthesis of the spiro-oxazolidinediones and spiro-**thiazolidinediones** (see II) generally have common synthetic intermediates. For example, spiro-tricyclic-oxazolidinedione derivative (6) is prepared from the tricyclic .alpha.-hydroxy ester, 2-fluoro-9-hydroxy-9H-fluorene-9-carboxylic acid methyl ester, which is an intermediate in the synthesis of spiro-tricyclic-**thiazolidinedione** (12). Reaction of the .alpha.-hydroxy ester with 1 or 2 (preferably 1.1) equivalents of urea and 1 to 2 (preferably. . .

SUMM . . . analogs of fluorene of Formula III, wherein A and B are previously defined. The synthesis of the spiro-tricyclicsuccinimides, spiro-oxazolidinediones and spiro-**thiazolidinediones** generally have common synthetic intermediates. For example, spiro-tricyclicsuccinimide derivatives (20) and (21) are prepared from the tricyclic acid esters, 9H-fluorene-9-carboxylic. . .

SUMM The novel spiro-tricyclic-imidazolidinediones, -**thiazolidinediones**, -oxazolidinediones and -succinimides may be further derivatized according to the following.

SUMM . . . acid and 60% sulfuric acid) of the spiro-cyclic derivatives, especially spiro-hydantoin (see Example XI). After nitration of the selected spiro-tricyclic-imidazolidinediones, -**thiazolidinediones**, -oxazolidinediones and succinimides by methods well known and practiced in the art, the corresponding aromatic nitro group(s) of corresponding spiro-tricyclic. . .

SUMM (c) Oxidation by selenium dioxide in a sealed vessel at 200.degree.-250.degree. C. when common oxidation procedures such as **chromium** trioxide in acetic acid are ineffective. See Arcus and Barnett, J. Chem. Soc. (1960) 2098.

SUMM . . . sodium, potassium, calcium, magnesium, etc. These pharmacologically acceptable nontoxic salts can be prepared by treating the aforementioned acidic specie, e.g., spiro-**thiazolidinedione**, with aqueous metallic hydroxide solution, and then evaporating the resulting solution, preferably at reduced pressure, to dryness. Alternatively, where indicated,. . .

SUMM As previously indicated, the spiro-tricyclic-**thiazolidinedione**, -imidazolidinedione, -oxazolidinedione and -succinimide compounds of this invention are all readily adapted to therapeutic use as aldose reductase inhibitors for. . .

SUMM . . . of the clinician, long term, prophylactic administration of the compounds of the present invention is generally indicated on diagnosis of **diabetes** mellitus and/or neuropathy and/or retinopathy and/or vasculopathy and/or cataract and/or impaired wound healing and/or nephropathy and/or hyperglyceamia.

SUMM . . . e.g., 6-fluoro-8H-indeno[2,1-b]thiophen-8-carboxylic acid methyl ester. The ester is utilized according to Methods II, III and IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidine-dione and spiro-succinimide such as spiro-(6-fluoro-8H-indeno[2,1-b]thiophen-8,5'-thiazolidine)-2',4'-dione, spiro-(6-fluoro-8H-indeno-8,5'-oxazolidine)-2,4'-dione and spiro-(6-fluoro-8H-indeno[2,1-b]thiophen-8,3'-succinimide) respectively.

SUMM . . . e.g., 6-chloro-4H-indeno[1,2-b]thiophen-4-carboxylic acid methyl ester. The ester is utilized according to Methods II, III and IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide such as spiro-(6-chloro-4H-indeno[1,2-b]thiophen-4,5'-thiazolidine]-2',4'-dione, spiro-(6-chloro-4H-indeno[1,2-b]thiophen-4,5'-oxazolidine)-2',4'-dione and spiro-(6-chloro-4H-indeno[1,2-b]thiophen-4,3'-succinimide) respectively. The resulting spiro-derivatives may be further derivatized according to. . .

SUMM . . . (and optional derivatization according to Method V) and spiro-derivatization in accordance with Methods II, III and IV yields the corresponding spiro-**thiazolidinedione**, spiro-oxazolidine-dione and spiro-succinimide derivatives respectively. These spiro-derivatives may be further derivatized according to Method VI.

SUMM . . . substrate 7H-cyclopenta[1,2-b:4,3-b']dithiophene is prepared according to the method of Wynberg and Kraak, J. Org. Chem., 29, 2455 (1964). The corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives are prepared according to Methods II-IV respectively. The 7-one derivative is prepared from the cyclopentadithiophene in. . .

SUMM . . . and 7H-cyclopenta[2,1-b:3,4-c']dithiophene are prepared according to the procedure of Wiersema and Wynberg, Tetrahedron, 24, 3381 (1968). From these, the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives are prepared according to Methods II-IV respectively. The corresponding 4H-cyclopenta[2,1-b:3,4-b']dithiophen-4-one, 7H-cyclopenta[1,2-b:3,4-b']dithiophen-7-one, 7H-cyclopenta[1,2-c:3,4-c']dithiophen-7-one, 7H-cyclopenta[1,2-b:3,4-c']dithiophen-7-one and 7H-cyclopenta[2,1-b:3,4-c']dithiophen-7-one are. . .

SUMM . . . 9, 849 (1978) to yield the corresponding 5H-indeno[1,2-c]pyridine which is derivatized in accordance with Methods II-IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide respectively. The aforementioned spiro-derivatives may be further derivatized according to Method VI.

SUMM . . . accordance with Method V. The resulting indenopyridine or 2-azafluorene product is further derivatized according to Methods II-IV to yield the spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives. Oxidation of the indenopyridine to the corresponding ketone is accomplished by sodium dichromate or other oxidation. . .

SUMM . . . 7-fluoro-1-azafluorene. The 9H-indeno [2,1-b]pyridine and its derivatives (e.g., 7-fluoro-9H-indeno[2,1-b]pyridine) are converted in accordance with Method II, III and IV into spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide

derivatives. The 9H-indeno[2,1-b]pyridine is oxidized according to general procedures cited in Method VII or potassium permanganate (Urbina,. . .

SUMM . . . the corresponding diazafluorene substrates such as 5H-cyclopenta[2,1-b:4,3-b']pyridine. These diazafluorene substrates are derivatized according to Methods II-IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide derivatives.

SUMM . . . yields the corresponding 8H-indeno[2,1-b]furan derivative which can be derivatized in accordance with Methods II, III and IV into the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide. Furthermore, the spiro-derivatives may be further derivatized according to Method VI.

SUMM . . . Method V. The derivatized or underivatized 4H-indeno [1,2-b]furan according to Method II, III and IV is derivatized to the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide respectively.

SUMM . . . derivatized or underivatized heterocycle then may be further derivatized according to Methods II, III or IV to yield the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione or spiro-succinimide respectively. These spiro-derivatives in turn may be derivatized in accordance with Method VI.

SUMM . . . be further derivatized in accordance with Method V and according to Methods II, III and IV derivatized into the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimides respectively. These spiro derivatives in turn may be further derivatized according to Method VI. Oxidation of the. . .

SUMM . . . 4H-thieno-pyrrolizines quantitatively. The resulting thieno[2,3-b]pyrrolizine and thieno[3,2-b]pyrrolizine can be derivatived according to Methods II, III and IV into the corresponding spiro-**thiazolidinediones**, spiro-oxazolidinediones and spiro-succinimides, such as spiro-(thieno[3,2-b]pyrrolizin-4,5'-thiazolidine)-2',4'-dione, spiro-(thieno[2,3-b]pyrrolizin-4,5'-oxazolidine)-2',4'-dione and spiro-(thieno[3,2-b]pyrrolizin-4,3'-succinimide).

SUMM After spiro-derivatization the corresponding spiro-hydantoin, spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide products are obtained.

SUMM . . . to the spiro-hydantoin. Alternately the heterocycle may be derivatized in accordance with Methods II, III and IV to the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide. These may be further derivatized in accordance with Method VI.

DETD . . . Calc. %C 67.40, %H 3.39; %N 5.24; meas. %C 67.46, %H 3.34, N 5.32. For the hydrolysis of 2-amino-4-thiazolones to **thiazolidinediones** using methanolic hydrogen chloride, see: Koltai, Tetrahedron (1973) 29, 2781.

DETD The product (50) can be derivatized in accordance with Methods II, III and IV into the corresponding spiro-**thiazolidinedione**, spiro-oxazolidinedione and spiro-succinimide.

DETD . . . moles of sodium hydroxide and then freeze-drying the mixture. In this way, the desired alkali metal salt of the spiro-hydantoin, spiro-**thiazolidinedione**, spiro-oxazolidinedione or spiro-succinimide can be prepared. In those cases where the aromatic substituents contain carboxylic acid moieties (e.g., isopropanoic acid. . .

DETD . . . containing 10, 25 and 200 mg of active ingredient, respectively, by merely using an appropriate quantity by weight of the spiro-**thiazolidinedione** in each case. Likewise other related examples of spiro-thiazoidinediones, spiro-imidazolidine-diones, spiro-oxazolidinediones, spiro-succinimides can be formulated as tablets on a respective. . .

AN 89:74287 USPATFULL
TI Spiro-tricyclicaromatic succinimide derivatives
IN York, Jr., Billie M., Fort Worth, TX, United States
PA Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)
PI US 4864028 19890905 <--
AI US 1987-94636 19870909 (7)
DCD 20020827
RLI Continuation-in-part of Ser. No. US 1987-5859, filed on 21 Jan 1987, now abandoned which is a continuation of Ser. No. US 1985-766569, filed on 14 Aug 1985, now abandoned which is a continuation of Ser. No. US 1983-532168, filed on 14 Sep 1983, now patented, Pat. No. US 4537892
DT Utility
FS Granted
EXNAM Primary Examiner: Schwartz, Richard A.
LREP Arno, James A., Brown, Gregg C., Price, Robert L.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3105
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 12 OF 13 USPATFULL
TI **Thiazolidinedione** derivatives, their production and use
PI US 4725610 19880216 <--
AB **Thiazolidinedione** derivatives of the general formula: ##STR1## [wherein R.sup.1 is hydrogen or a hydrocarbon residue or heterocyclic residue which may each. . . are novel compounds, possess blood-glucose and blood-lipid lowering actions in mammals, and are of value as a therapeutic agent for **diabetes** and therapeutic agent for hyperlipemia.
SUMM This invention relates to novel **thiazolidinedione** derivatives which possess blood-glucose and blood-lipid lowering actions, to processes for producing the same and to pharmaceutical compositions containing the. . .
SUMM As a therapeutic agent for **diabetes**, heretofore, there have been used various biguanide and sulfonylurea compounds. However, the biguanide compounds are hardly in current use, because. . . severe hypoglycemia, thus requiring careful precautions on the occasion of their use. The development of a novel therapeutic agent for **diabetes** which is free from such defects is desired. In Japanese Unexamined Patent Publication Nos. 22636/1980 and 64586/1980, Chemical & Pharmaceutical. . . (1982), ibid. 30, 3580 (1982) and ibid., 32, 2267 (1984), on the other hand, there is a description that various **thiazolidinediones** exhibit blood-lipid and blood-glucose lowering actions, and in **Diabetes**, 32, 804 (1983), futhermore, there has been provided a description of the antidiabetic action demonstrated by ciglitazone. Nevertheless, all of these compounds has failed so far to be commercialized as a therapeutic agent for **diabetes**. The present inventors conducted repeated research on **thiazolidinediones**, and as a result, found entirely novel derivatives which possess outstandingly potent blood-glucose and blood-lipid lowering actions and can be. . .
SUMM 1. A **thiazolidinedione** derivative of the general formula: ##STR2## [wherein R.sup.1 is hydrogen or a hydrocarbon residue or heterocyclic residue which may each. . .
SUMM 9. A method for the treatment of **diabetes** or hyperlipemia, which comprises administering to a mammal suffering from the disease a compound of the formula (I) or its. . .
SUMM . . . hours. The chromic acid oxidation can be allowed to proceed by means of the methods of utilizing a Jones reagent (**chromium** trioxide-sulfuric acid-acetone) in **chromium** trioxide in acetic

acid, **chromium** trioxide in pyridine or a previously prepared **chromium** trioxidepyridine complex in dichloromethane used as a solvent. The amount of **chromium** (VI) to be used is normally 0.5 to 2 equivalents against Compound (I-3). The reaction temperature is -10.degree. C. to. . .

SUMM The **thiazolidinedione** derivative (I) and its salts as obtained in this manner can be isolated and purified by the known separation and. . .

SUMM . . . and human being), and show a low degree of toxicity in terms of both acute and subacute toxicities. Therefore, the **thiazolidinedione** derivative (I) and its salts is of value to human beings for the treatment of hyperlipemia, **diabetes** and their complications. With reference to the method of administration, they are normally used orally in such dosage forms as. . . injectable solutions, suppositories and pellets, as the case may be. In the case of application as a therapeutic agent for **diabetes** or hyperlipemia, the compounds can be nomally administered to an adult patient orally at a dose of 0.003 to 10. . .

DETD To a solution of 5-(4-hydroxybenzyl)-2,4-**thiazolidinedione** (9.4 g) in N,N-dimethylformamide (80 ml) was added 60% sodium hydride in oil (3.4 g), and the mixture was stirred. . . mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried (MgSO.sub.4) and concentrated to give 5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione** (9.1 g, 47.4%). Recrystallization from ethanol yielded colorless needles. m.p. 188.degree.-189.degree. C. Elemental analysis for C.sub.20 H.sub.16 N.sub.2 O.sub.4 S;. . .

DETD 60% sodium hydride in oil (1.32 g) was added to solution of 5-(4-hydroxybenzyl)-2,4-**thiazolidinedione** (3.35 g) in N,N-dimethylformamide (30 ml), and the mixture was stirred for 30 minutes. Then, solution of 4-chloromethyl-2-(1-methylcyclohexyl)oxazole (3.85 g). . . The oily residue was chromatographed on a column of silica gel (70 g). Elution with hexaneethyl acetate (2:1, V/V) gave 5-{4-[2-(1-methylcyclohexyl)-4-oxazolylmethoxy]benzyl}-2,4-**thiazolidinedione** as an oily substance. A solution of sodium 2-ethylhexanoate in isopropanol (2N, 3 ml) was added to the oily substance, and treated with ether. The crystals which separated out were collected by filtration to give 5- {4-[2-(1-methylcyclohexyl)-4-oxazolylmethoxy]benzyl}-2,4-**thiazolidinedione**.sodium salt (2.3 g, 36.3%). Recrystallization from methanol afforded colorless plates. m.p. 285.degree.-287.degree. C. (decomp.) Elemental analysis for C.sub.21 H.sub.23 N.sub.2. . .

DETD . . . and extracted with chloroform. The chloroform layer was washed with water and dried (MgSO.sub.4). The solvent was distilled off, whereby 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione** (18.0 g, 95.7%) was obtained. Recrystallization from ethanol afforded colorless needles. m.p. 113.degree.-114.degree. C. Elemental Analysis for C.sub.22 H.sub.20 N.sub.2. . .

DETD . . . on a column of silica gel (200 g), and from the fractions eluted with chlorform-methanol (100:1, V/V), there was obtained 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-**thiazolidinedione** (6.7 g, 58.8%). Recrystallization from ethyl acetate-hexane afforded colorless plates. m.p. 162.degree.-163.degree. C. Elemental analysis for C.sub.21 H.sub.18 N.sub.2 O.sub.4. . .

DETD . . . was added to the solution, and the crystals which separated out were collected by filtration and recrystallization from ethanol gave 5<4-{2-[5-methyl-2-(1-methylcyclohexyl)-4-oxazolyl]ethoxy}benzyl>-2,4-**thiazolidinedione**.sodium salt (5.1 g, 51.5%). Colorless prisms, m.p. 250.degree.-251.degree. C. (decomp.). Elemental analysis for C.sub.23 H.sub.27 N.sub.2 O.sub.4 SNa, Calcd.: C,. . .

DETD (1) N-Bromosuccinimide (2.75 g) was added portionwise to a solution of

5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione** (6.0 g) and .alpha.,.alpha.'-azobisisobutyronitrile (0.5 g) in carbon tetrachloride(150 ml) under reflux. After refluxing for another 10 minutes, the reaction mixture was washed with water and dried (MgSO.sub.4). The solvent was distilled off to give 5-{4-[2-(5-bromomethyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione** as a crude oily substance (about 8 g). IR (neat) cm.sup.-1 : 1750, 1690. NMR.delta.(ppm) in CDCl.sub.3 : 3.03 (2. . .

DETD . . . chromatographed on a column of silica gel (200 g). From the fractions eluted with ether-hexane (1:1, V/V), there was obtained 5-{4-[2-(5-hydroxymethyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione** (1.31 g, 21.0%). Recrystallization from acetone-hexane yielded colorless scales. m.p. 98.degree.-99.degree. C. Elemental analysis for C.sub.22 H.sub.20 N.sub.2 O.sub.5 S,. . .

DETD By a procedure similar to that of Example 1, there was obtained 5-[4-(4-thiazolylmethoxy)benzyl]-2,4-**thiazolidinedione**. Yield of 18.1%. Recrystallization from acetone-hexane afforded colorless needles, m.p. 151.degree.-153.degree. C. Elemental analysis for C.sub.14 H.sub.12 N.sub.2 O.sub.3 S.sub.2,. . .

DETD By a procedure similar to that of Example 34, there was obtained 5-<4-{2-[5-methyl-2-(1-methyl-3-cyclohexenyl)-4-oxazolyl]ethoxy}benzyl>-2,4-**thiazolidinedione**.sodium salt. Yield 79.2%. Recerystallization from methanol-ethyl acetate afforded colorless prisms. m.p. 245.degree.-246.degree. C. (decomp.). Elemental analysis for C.sub.23 H.sub.25 N.sub.2. . .

DETD Acetic anhydride (1.0 ml) was added to a solution of 5-{4-[2-(2,5-dimethyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-**thiazolidinedione** (0.5 g) in dimethylsulfoxide (10 ml), and the mixture was allowed to stand overnight and poured into water. The mixture. . . on a column of silica gel (40 g), and from the fractions eluted with benzene-acetone (9:1 V/v), there was obtained 5-{4-[2-(2,5-dimethyl-4-oxazolyl)-2-oxoethoxy]benzyl}-2,4-**thiazolidinedione** (0.24 g, 48.3%). Recrystallization from ethyl acetate-hexane afforded colorless plates, m.p. 161.degree.-162.degree. C. Elemental analysis for C.sub.17 H.sub.16 N.sub.2 O.sub.5. . .

DETD By a procedure similar to that of Example 47, there was obtained 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzyl}-2,4-**thiazolidinedione**. Yield 81.3% Recrystallization from ethyl acetate-hexane afforded colorless prisms, m.p. 168.degree.-169.degree. C.

DETD A mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (5.0 g), 2,4-**thiazolidinedione** (3.8 g), piperidine (0.32 ml) and ethanol (100 ml) was stirred under reflux for 5 hours. After cooling, the crystals which separated out were collected by filtration to give 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione** (5.1 g, 76.8%). Recrystallization from chloroform-ethanol afforded colorless needles, m.p. 213.degree.-214.degree. C. Elemental analysis for C.sub.22 H.sub.18 N.sub.2 O.sub.4 S,. . .

DETD 60% sodium hydride in oil (0.24 g) was added to a solution of 5-(4-hydroxybenzylidene)-2,4-**thiazolidinedione** (0.664 g) in N,N-dimethylformamide (20 ml), and the mixture was stirred for 30 minutes. A solution of 4-chloromethyl-5-methyl-2-phenyloxazole (0.623 g). . . on a column of silica gel (50 g). From the fractions eluted with ethyl acetatehexane (1:2, V/V), there was obtained 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzylidene]-2,4-**thiazolidinedione** (0.49 g, 40.8%). Recrystallization from chloroform-methanol afforded colorless prisms, m.p. 225.degree.-226.degree. C. Elemental analysis for C.sub.21 H.sub.16 N.sub.2 O.sub.4 S,. . .

DETD 60% sodium hydride in oil (0.24 g) was added to a solution of

5-(4-hydroxybenzylidene)-2,4-**thiazolidinedione** (0.663 g) in N,N-dimethylformamide (20 ml) and the mixture was stirred for 30 minutes. Then, a solution of 4-bromoacetyl-5-methyl-2-phenyloxazole (0.841. . . with acetic acid. The solid which precipitated was collected by filtration, washed with water, and crystallized from acetone to give 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzylidene}-2,4-**thiazolidinedione** (0.42 g, 32.3%). Recrystallization from chloroform-ethanol yielded colorless needles, m.p. 244.degree.-245.degree. C. Elemental analysis for C.sub.22 H.sub.16 N.sub.2 O.sub.5 S,. . .

DETD Sodium borohydride (0.16 g) was added to a suspension of 5-{4-[2-(2,5-dimethyl-oxazolyl)-2-oxoethoxy]benzylidene}-2,4-**thiazolidinedione** (1.5 g) in methanol-N,N-dimethylformamide (1:1, V.V, 40 ml) under ice-cooling. After stirring under ice-cooling for 20 minutes, the reaction solution. . . aqueous mixture was made acid with acetic acid, and the crystals which separated out were collected by filtration to give 5-{4-[2-(2,5-dimethyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-**thiazolidinedione** (1.47 g, 97.5%). Recrystallization from chloroform-ethanol afforded colorless prisms, m.p. 223.degree.-224.degree. C. Elemental analysis for C.sub.17 H.sub.16 N.sub.2 O.sub.5 S,. . .

DETD By a procedure similar to that of Example 66, there was obtained 5-{4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione** (the same compound as that obtained in Example 61 from 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzylidene}-2,4-**thiazolidinedione**. M.p. 252.degree.-253.degree. C. Yield 98.4%.

DETD 0.32 ml of 28% sodium methylate in methanol was added dropwise to a suspension of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione** (0.50 g) in methanol (10 ml). The reaction solution was concentrated, and diluted with ehyl ether. The crystals which separated out were collected by filtration to give sodium salt (0.43 g, 81.6%) of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione**. Recrystallization from methanol afforded colorless prisms, m.p. 286.degree.-288.degree. C. (decomp.). Elemental analysis for C.sub.22 H.sub.17 N.sub.2. O.sub.4 SNa, Calcd.: C,. . .

DETD A stirred mixture of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione** (500 mg), 10% Pd-C (50% wet, 1.0 g) and acetic acid (50 ml) was hydrogenated at 70.degree. C. and at. . . and water, and dried over magnesium sulfate. The solvent was removed and the residue was recrystallized from ethanol to yield 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione** (the same compound as that obtained in Example 12) as crystals (415 mg, 82.7%). m.p. 113.degree.-114.degree. C.

DETD A stirred mixture of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzylidene}-2,4-**thiazolidinedione** (1.0 g), Pd-black (3 g) and dioxane (100 ml) was hydrogenated at 40.degree. C. and at atmospheric pressure. After 4. . . added and hydrogenation was continued for 4 hours. The catalyst was filtered off and the filtrate was concentrated to yield 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzyl}-2,4-**thiazolidinedione** (the same compound as that obtained in Example 48) as crystals (0.95 g, 94.1%). Recrystallization from ethyl acetate-hexane gave colorless. . .

DETD A solution of (Z)-5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione** (200 mg) in acetonitrile (750 ml), in a quartz tube under a stream of nitrogen, was irradiated by a 300. . . the resulting crystals were chromatographed on a column of silica gel (200 g). Elution with hexane-ethyl acetate (1:1, V/V) gave (E)-5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione** (40 mg, 20.0%). Recrystallization from dichloromethaneethanol yielded colorless

needles, m.p. 216.degree.-217.degree. C. Elemental analysis for C.sub.22 H.sub.18 N.sub.2 O.sub.4 S;. . . 6.89. Found: C, 64.69; H, 4.26; N, 7.11. The subsequent elution with hexane-ethyl acetate (1:1, V/v) allowed the recovery of (Z)-5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione** (138 mg, 69.0%).

DETD . . . -- 51****

64 26**** 59**** 37* 61****

Control compound:

Ciglitazone.sup.1 -- 10 -- -13

t-test; *P 0.05, **P 0.02, ***P 0.01, ****P 0.001

.sup.1 5-[4-(1-Methylcyclohexylmethxoy)]benzyl-2,4-**thiazolidinedione**

DETD

Tablet Production Example

(a)	(1)	5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]benzyl}-2,4-**thiazolidinedione**	10 g
	(2)	Lactose	50 g
	(3)	Corn starch	15 g
	(4)	Carboxymethylcellulose calcium	44 g
	(5)	Magnesium stearate	1 g
			120. . .

DETD

(b)	(1)	5-{4-[2-(5-Methyl-2-phenyl-4-oxazolyl)-ethoxy]benzylidene}-2,4-**thiazolidinedione**	30 g
	(2)	Lactose	50 g
	(3)	Corn starch	15 g
	(4)	Carboxymethylcellulose calcium	44 g
	(5)	Magnesium stearate	1 g
			140. . .

CLM What is claimed is:

8. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-**thiazolidinedione**.

9. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-**thiazolidinedione**.

10. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-**thiazolidinedione**

11. A pharmaceutical composition which contains a **thiazolidinedione** derivative of the formula: ##STR133## wherein R.sup.1 is hydrogen, a hydrocarbon residue having 1 to 13 carbon atoms or a. . .

12. A method for the treatment of **diabetes** or hyperlipemia, which comprises administering to a mammal suffering from **diabetes** or hyperlipemia a compound of the formula: ##STR134## wherein R.sup.1 is hydrogen, a hydrocarbon residue having 1 to 13 carbon. . .

AN 88:9924 USPATFULL|

TI **Thiazolidinedione** derivatives, their production and use|
IN Meguro, Kanji, Nishinomiya, Japan
Fujita, Takeshi, Takarazuka, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 4725610 19880216 <--
AI US 1985-783628 19851003 (6)
PRAI WO 1984-JP466 19841003
WO 1985-JP179 19850409
DT Utility|
FS Granted|
EXNAM Primary Examiner: Gerstl, Robert|
LREP Wenderoth, Lind & Ponack|
CLMN Number of Claims: 12|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 1662|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 13 OF 13 USPATFULL
PI US 4556670 19851203 <--
AB . . . are disclosed which are useful as aldose reductase inhibitors and as therapeutic agents for the treatment of complications arising from **diabetes**. Pharmaceutical compositions containing the spiro compounds and a method of treating diabetic complications are also disclosed.
SUMM This invention relates to novel spiro-3-heteroazolidindiones useful in the treatment of certain chronic complications arising from **diabetes** mellitus, such as diabetic cataracts, retinopathy and neuropathy, to pharmaceutical compositions containing such compounds and to a method of using. . .
SUMM . . . when administered orally. However, little is known about the effect of organic compounds in preventing or alleviating chronic complications of **diabetes**, such as diabetic cataracts, neuropathy and retinopathy. U.S. Pat. No. 3,821,383 discloses aldose reductase inhibitors like 1,3-dioxo-1H-benz[d,e]-isoquinoline-2(3H)-acetic acid and derivatives. . . for the treatment of these conditions. U.S. Pat. No. 4,117,230 teaches the use of certain hydantoins for treating complications of **diabetes** as aldose reductase inhibitors. Such aldose reductase inhibitors function by inhibiting the activity of the enzyme aldose reductase, which is. . .
SUMM The present invention further comprises a method of treating a diabetic host for **diabetes**-associated complications which comprises administering to the host an effective amount of a compound of formula I. A preferred method is. . .
SUMM . . . hydroxymethylene) may be further oxidized to the corresponding ketone (I, W is carbonyl) using any convenient oxidizing agent such as **chromium** trioxide in acetic acid at about 0.degree. to 60.degree. C., preferably about 25.degree. C.
SUMM . . . preparation of compounds of formula I wherein U is O. These cyanotrialkylsilyloxy derivatives may be converted by similar methods to **thiazolidinedione** intermediates of structure II wherein U is S (Synthetic Scheme A) and intermediates of structure V wherein U is S. . .
SUMM . . . pharmaceutically acceptable salts thereof are useful as inhibitors of the enzyme aldose reductase in the treatment of chronic complications of **diabetes**, such as diabetic cataracts, retinopathy and neuropathy. As used in the claims and specification hereof, treatment is meant to include. . .
DETD 3'-Hydroxy-spiro[imidazolidine-4,1'-indan]2,5-dione (1.2 g, 5.5 mmol) was combined with 0.550 g (5.5 mmol) of **chromium** trioxide in 20 ml glacial acetic acid at 25.degree. C. As dissolution occurred the reaction mixture darkened and the temperature. . .

DETD 3'-Hydroxy-6'-fluoro-spiro[imidazolidine-4,1'indan]-2,5-dione (1.0 g, 4.2 mmol) was combined with 0.424 g (4.2 mmol) **chromium** trioxide in 25 ml glacial acetic acid and was heated at 100.degree. C. for 1 hour. The reaction was concentrated. . .

DETD 4'-Hydroxy-spiro[imidazolidine-4,1'-1',2',3',4'-tetrahydronaphthalene]2,5-dione (10.0 g, 43.1 mmol) was combined with 4.34 g (43.4 mmol) of **chromium** trioxide in 80 ml glacial acetic acid and stirred at 25.degree. C. for 1 hour. The reaction mixture was concentrated. . .

DETD 40.45 g (0.153 mol) of (+)7'-Fluoro-4'-hydroxy-3'-methyl-spiro[imidazolidine-4,1'-1',2',3',4'-tetrahydronaphthalene]2,5-dione was combined with 15.31 g (0.153 mol) **chromium** trioxide in 250 ml glacial acetic acid and the reaction temperature was maintained at 25.degree. C. After 1.5 hours the. . .

DETD 39.6 g (0.15 mol) of (-) 7'-Fluoro-4'-hydroxy-3'-methyl-spiro[imidazolidine-4,1'-1',2',3',4'-tetrahydronaphthalene]2,5-dione was combined with 15.0 g (0.15 mol) of **chromium** trioxide in 200 ml of glacial acetic acid and stirred at 25.degree. C. with some cooling required until the initial,. . .

DETD . . . 5 ml ethyl acetate and 1 ml glacial acetic acid. To this solution was added 180 mg (0.4 mmol) of **chromium** trioxide and the resulting green solution was stirred at 25.degree. C. for 2.5 hours. Thin layer chromatographic analysis (silica gel-ethyl. . .

CLM What is claimed is:

. . . diluent and a compound as claimed in claim 1 in an amount effective for the treatment of ocular or neuritic **diabetes**-associated chronic complications.

55. A method for treating a diabetic host to prevent or alleviate ocular or neuritic **diabetes**-associated chronic complications, which comprises orally, parenterally or topically administering to said diabetic host an alleviating or prophylactically effective amount of. . .

AN 85:70919 USPATFULL|

TI Spiro-3-hetero-azolones for treatment of diabetic complications|

IN Lipinski, Christopher A., Waterford, CT, United States

PA Pfizer Inc., New York, NY, United States (U.S. corporation)

PI US 4556670 19851203 <--

AI US 1983-545450 19831028 (6)

RLI Continuation-in-part of Ser. No. US 1982-447337, filed on 6 Dec 1982, now abandoned

DT Utility|

FS Granted|

EXNAM Primary Examiner: Gerstl, Robert|

LREP Knuth, Charles J., Richardson, Peter C.|

CLMN Number of Claims: 60|

ECL Exemplary Claim: 1|

DRWN No Drawings

LN.CNT 1601|

CAS INDEXING IS AVAILABLE FOR THIS PATENT.